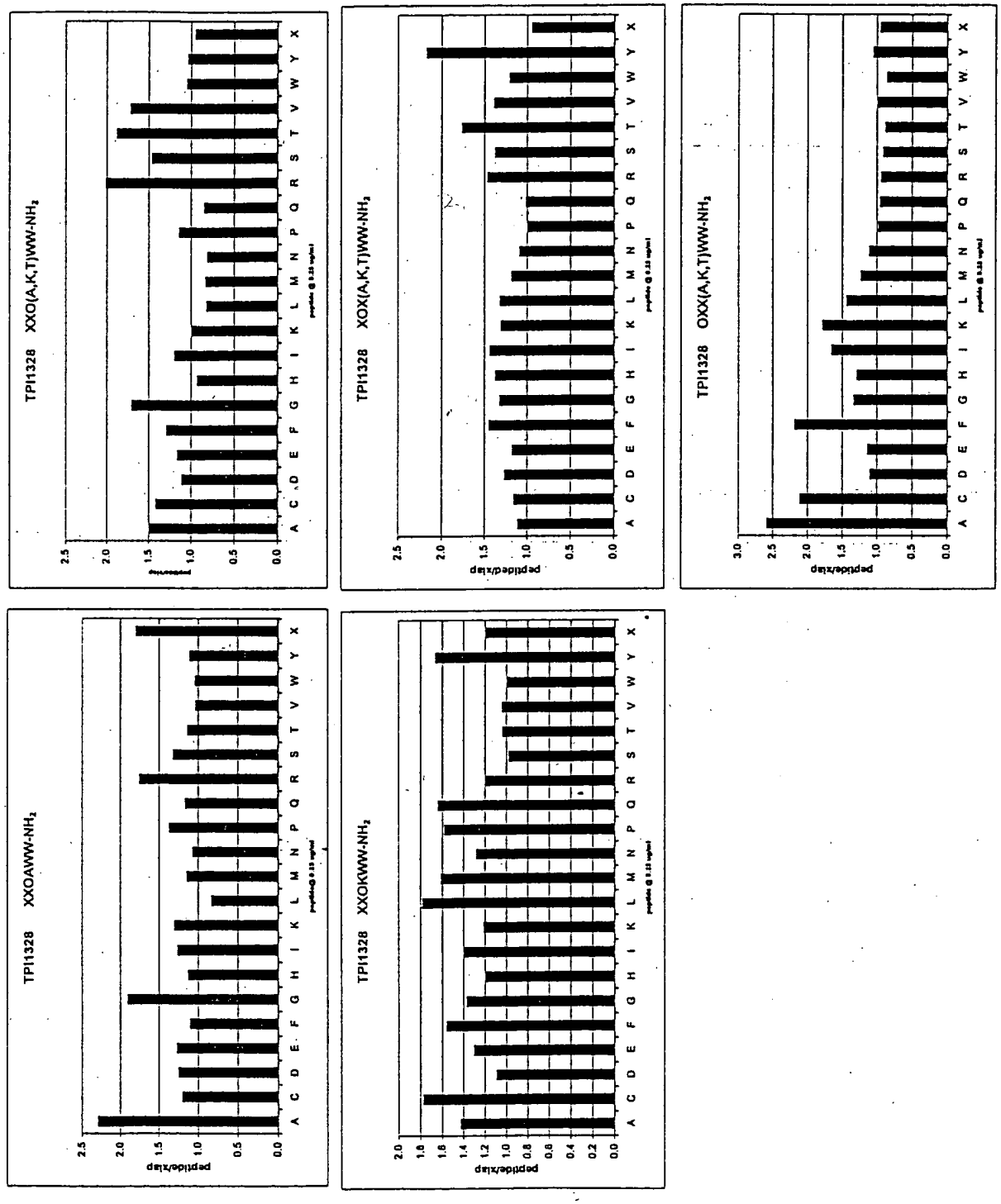

TPI1328 XXO(A,K,T)WW-NH2
TPI1328 XOX(A,K,T)WW-NH2
TPI1328 OXX(A,K,T)WW-NH2
TPI1328 XXOAWW-NH2
TPI1328 XXOKWW-NH2
peptide/xlap
A C D E F G H I K L M N P Q R S T V W Y X

FIGURE 1

TPI 1313

	1	2	3	4					
	L-Thiala	D-pCl-Phe	D-OEt-Tyr	D-pCl-Phe				Ratio>1.9	
	D-Thiala	D-OEt-Tyr	D-Nal	D-pNO2-Phe					
	Phe	D-Phe		D-Thiala					
						Ratio Caspase3/Xiap		Ratio peptide/xiap	
Vial#	1	2	3	4		Avg	std	AVG	std
1	L-Thiala	D-pCl-Phe	D-OEt-Tyr	D-pCl-Phe	-NH2	0.9	0.036	1.3	0.20
2	L-Thiala	D-pCl-Phe	D-OEt-Tyr	D-pNO2-Phe	-NH2	0.9	0.035	1.3	0.22
3	L-Thiala	D-pCl-Phe	D-OEt-Tyr	D-Thiala	-NH2	0.9	0.031	0.9	0.10
4	L-Thiala	D-pCl-Phe	D-Nal	D-pCl-Phe	-NH2	0.9	0.031	2.3	0.60
5	L-Thiala	D-pCl-Phe	D-Nal	D-pNO2-Phe	-NH2	0.9	0.033	1.7	0.24
6	L-Thiala	D-pCl-Phe	D-Nal	D-Thiala	-NH2	0.9	0.029	1.3	0.17
7	L-Thiala	D-OEt-Tyr	D-OEt-Tyr	D-pCl-Phe	-NH2	0.9	0.024	2.7	0.37
8	L-Thiala	D-OEt-Tyr	D-OEt-Tyr	D-pNO2-Phe	-NH2	0.9	0.027	1.4	0.21
9	L-Thiala	D-OEt-Tyr	D-OEt-Tyr	D-Thiala	-NH2	0.9	0.032	0.9	0.05
10	L-Thiala	D-OEt-Tyr	D-Nal	D-pCl-Phe	-NH2	0.9	0.029	0.7	0.09
11	L-Thiala	D-OEt-Tyr	D-Nal	D-pNO2-Phe	-NH2	0.9	0.031	0.9	0.18
12	L-Thiala	D-OEt-Tyr	D-Nal	D-Thiala	-NH2	0.9	0.029	0.9	0.13
13	L-Thiala	D-Phe	D-OEt-Tyr	D-pCl-Phe	-NH2	0.9	0.028	0.6	0.08
14	L-Thiala	D-Phe	D-OEt-Tyr	D-pNO2-Phe	-NH2	0.9	0.028	0.6	0.08
15	L-Thiala	D-Phe	D-OEt-Tyr	D-Thiala	-NH2	0.9	0.025	0.6	0.07
16	L-Thiala	D-Phe	D-Nal	D-pCl-Phe	-NH2	0.9	0.029	0.8	0.09
17	L-Thiala	D-Phe	D-Nal	D-pNO2-Phe	-NH2	0.9	0.032	1.1	0.10
18	L-Thiala	D-Phe	D-Nal	D-Thiala	-NH2	0.9	0.029	0.9	0.08
19	D-Thiala	D-pCl-Phe	D-OEt-Tyr	D-pCl-Phe	-NH2	0.9	0.031	1.5	0.24
20	D-Thiala	D-pCl-Phe	D-OEt-Tyr	D-pNO2-Phe	-NH2	0.8	0.042	1.3	0.30
21	D-Thiala	D-pCl-Phe	D-OEt-Tyr	D-Thiala	-NH2	0.9	0.030	0.9	0.10
22	D-Thiala	D-pCl-Phe	D-Nal	D-pCl-Phe	-NH2	0.9	0.030	1.0	0.14
23	D-Thiala	D-pCl-Phe	D-Nal	D-pNO2-Phe	-NH2	0.9	0.022	1.0	0.10
24	D-Thiala	D-pCl-Phe	D-Nal	D-Thiala	-NH2	0.9	0.024	1.3	0.16
25	D-Thiala	D-OEt-Tyr	D-OEt-Tyr	D-pCl-Phe	-NH2	1.0	0.028	1.6	0.20
26	D-Thiala	D-OEt-Tyr	D-OEt-Tyr	D-pNO2-Phe	-NH2	0.8	0.027	1.1	0.14
27	D-Thiala	D-OEt-Tyr	D-OEt-Tyr	D-Thiala	-NH2	0.9	0.037	1.1	0.12
28	D-Thiala	D-OEt-Tyr	D-Nal	D-pCl-Phe	-NH2	0.9	0.041	1.1	0.11
29	D-Thiala	D-OEt-Tyr	D-Nal	D-pNO2-Phe	-NH2	0.9	0.032	1.1	0.14
30	D-Thiala	D-OEt-Tyr	D-Nal	D-Thiala	-NH2	0.9	0.043	1.2	0.12
31	D-Thiala	D-Phe	D-OEt-Tyr	D-pCl-Phe	-NH2	0.9	0.038	1.3	0.15
32	D-Thiala	D-Phe	D-OEt-Tyr	D-pNO2-Phe	-NH2	1.0	0.036	1.1	0.08
33	D-Thiala	D-Phe	D-OEt-Tyr	D-Thiala	-NH2	0.9	0.034	1.0	0.08
34	D-Thiala	D-Phe	D-Nal	D-pCl-Phe	-NH2	0.9	0.027	1.0	0.13
35	D-Thiala	D-Phe	D-Nal	D-pNO2-Phe	-NH2	0.9	0.029	0.9	0.12
36	D-Thiala	D-Phe	D-Nal	D-Thiala	-NH2	0.9	0.032	1.1	0.13
37	Phe	D-pCl-Phe	D-OEt-Tyr	D-pCl-Phe	-NH2	0.9	0.042	1.3	0.14
38	Phe	D-pCl-Phe	D-OEt-Tyr	D-pNO2-Phe	-NH2	0.9	0.030	0.8	0.12
39	Phe	D-pCl-Phe	D-OEt-Tyr	D-Thiala	-NH2	0.9	0.029	0.9	0.11
40	Phe	D-pCl-Phe	D-Nal	D-pCl-Phe	-NH2	0.9	0.026	1.9	0.13
41	Phe	D-pCl-Phe	D-Nal	D-pNO2-Phe	-NH2	1.0	0.120	0.9	0.07
42	Phe	D-pCl-Phe	D-Nal	D-Thiala	-NH2	0.9	0.045	1.0	0.27
43	Phe	D-OEt-Tyr	D-OEt-Tyr	D-pCl-Phe	-NH2	1.0	0.098	0.9	0.14
44	Phe	D-OEt-Tyr	D-OEt-Tyr	D-pNO2-Phe	-NH2	1.0	0.139	1.0	0.07
45	Phe	D-OEt-Tyr	D-OEt-Tyr	D-Thiala	-NH2	1.0	0.114	0.8	0.23
46	Phe	D-OEt-Tyr	D-Nal	D-pCl-Phe	-NH2	1.0	0.124	0.9	0.26
47	Phe	D-OEt-Tyr	D-Nal	D-pNO2-Phe	-NH2	0.9	0.100	1.0	0.33
48	Phe	D-OEt-Tyr	D-Nal	D-Thiala	-NH2	1.0	0.068	1.0	0.05
49	Phe	D-Phe	D-OEt-Tyr	D-pCl-Phe	-NH2	1.0	0.057	1.1	0.09
50	Phe	D-Phe	D-OEt-Tyr	D-pNO2-Phe	-NH2	0.9	0.106	0.9	0.07
51	Phe	D-Phe	D-OEt-Tyr	D-Thiala	-NH2	1.0	0.056	0.9	0.03
52	Phe	D-Phe	D-Nal	D-pCl-Phe	-NH2	0.9	0.083	1.0	0.14
53	Phe	D-Phe	D-Nal	D-pNO2-Phe	-NH2	0.9	0.080	0.9	0.06
54	Phe	D-Phe	D-Nal	D-Thiala	-NH2	1.0	0.127	0.9	0.03

FIGURE 2

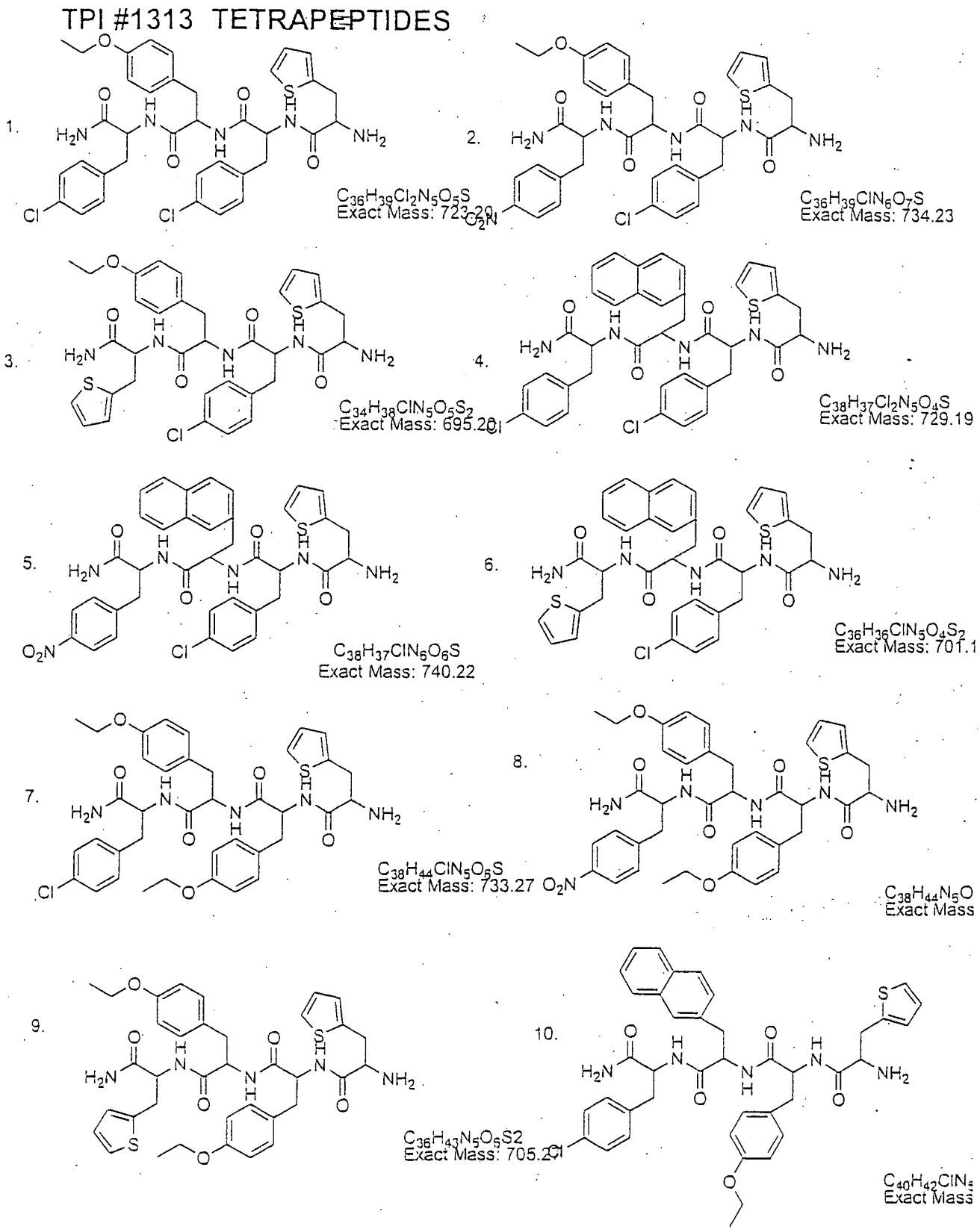
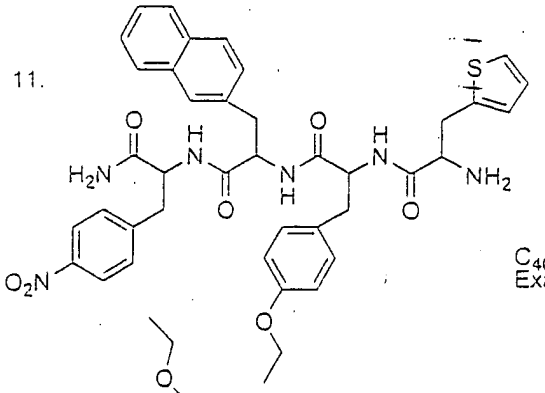

TPI #1313 TETRAPEPTIDES
1.
$C_{36}H_{39}Cl_2N_5O_5S$
Exact Mass: 723.20
2.
$C_{36}H_{39}ClN_6O_7S$
Exact Mass: 734.23
3.
$C_{34}H_{38}ClN_5O_5S_2$
Exact Mass: 695.20
4.
$C_{38}H_{37}Cl_2N_5O_4S$
Exact Mass: 729.19
5.
$C_{38}H_{37}ClN_6O_6S$
Exact Mass: 740.22
6.
$C_{36}H_{36}ClN_5O_4S_2$
Exact Mass: 701.1
7.
$C_{38}H_{44}ClN_5O_5S$
Exact Mass: 733.27
8.
$C_{38}H_{44}N_5O$
Exact Mass
9.
$C_{36}H_{43}N_5O_5S2$
Exact Mass: 705.2
10.
$C_{40}H_{42}ClN_5$
Exact Mass

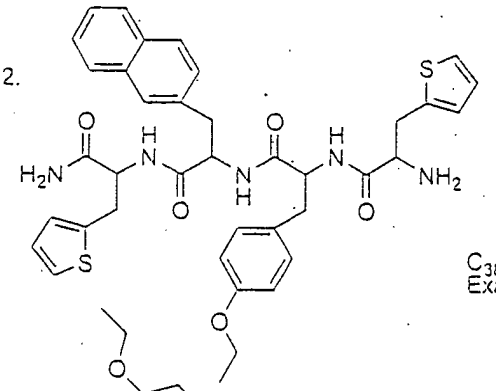
FIGURE 3A

11.



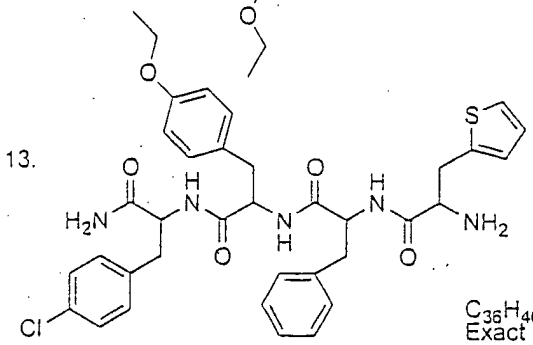
$C_{40}H_{42}N_6O_7S$
Exact Mass: 750.28

12.



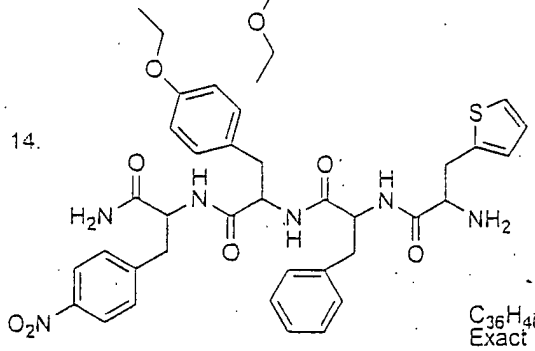
$C_{38}H_{41}N_5O$
Exact Mass

13.



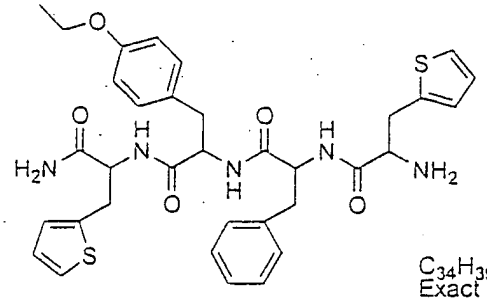
$C_{36}H_{40}ClN_5O_5S$
Exact Mass: 689.24

14.



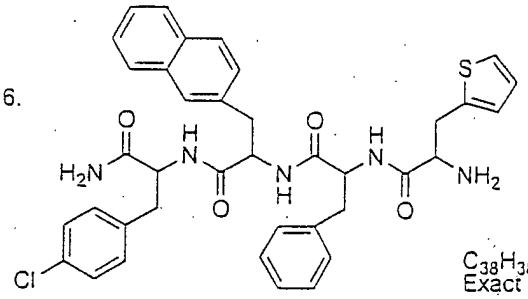
$C_{36}H_{40}N_6O_7S$
Exact Mass: 7(

15.



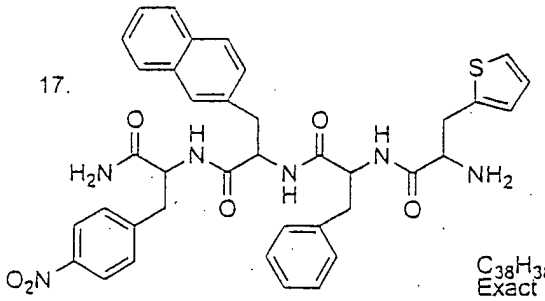
$C_{34}H_{39}N_5O_5S2$
Exact Mass: 661.24

16.



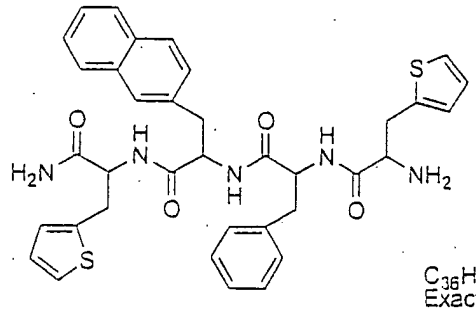
$C_{38}H_{38}ClN_5C$
Exact Mass:

17.



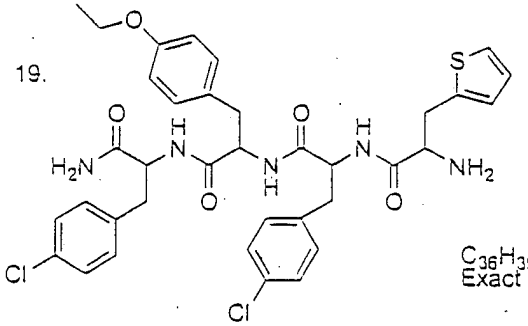
$C_{38}H_{38}N_6O_6S$
Exact Mass: 706.26

18.



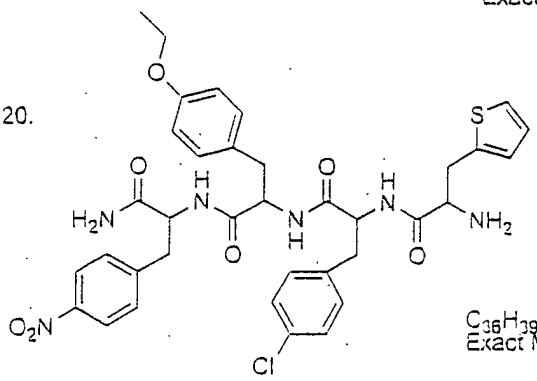
$C_{36}H_{37}N_5O_4$
Exact Mass:

19.



$C_{36}H_{39}Cl_2N_5O_5S$
Exact Mass: 723.20

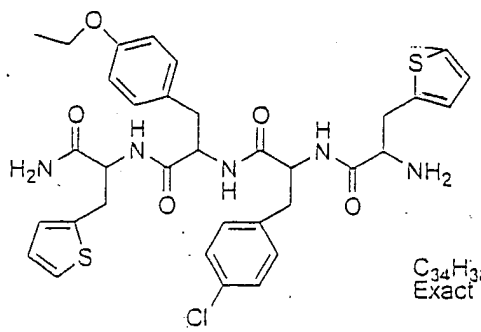
20.



$C_{36}H_{39}ClN_6O_$
Exact Mass: 7

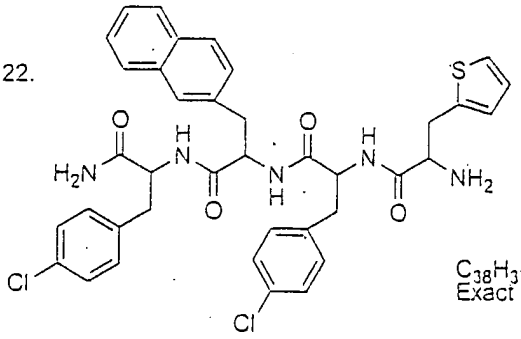
FIGURE 3B

21.



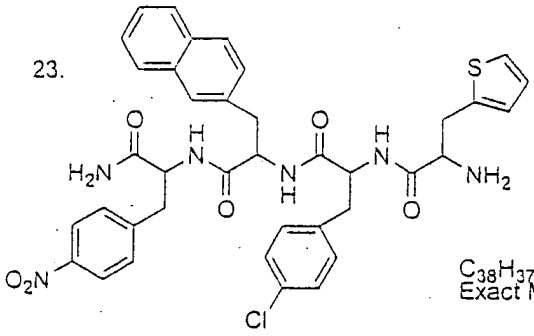
$C_{34}H_{38}ClN_5O_5S_2$
Exact Mass: 695.20

22.



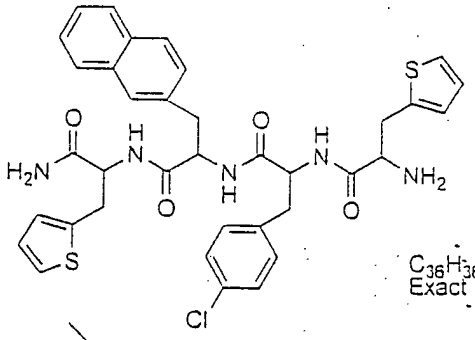
$C_{38}H_{37}Cl_2N_5O$
Exact Mass: 7

23.



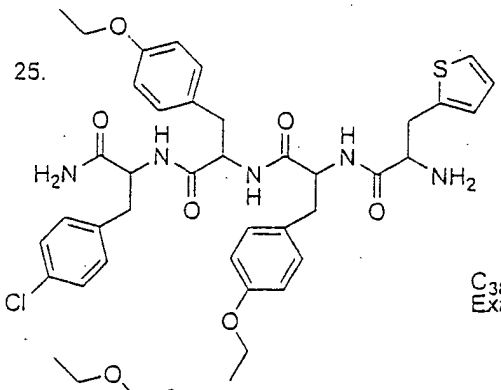
$C_{38}H_{37}ClN_6O_6S$
Exact Mass: 740.22

24.



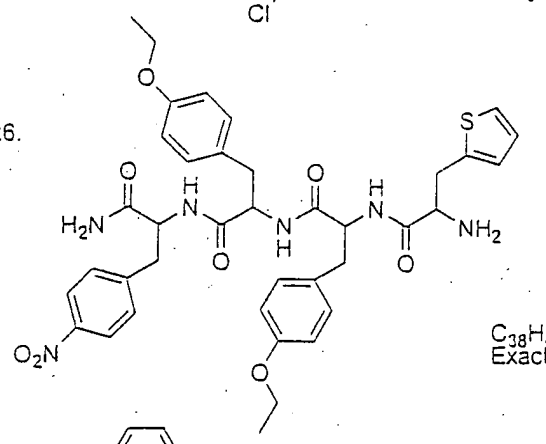
$C_{36}H_{36}ClN_5O_$
Exact Mass: 7

25.



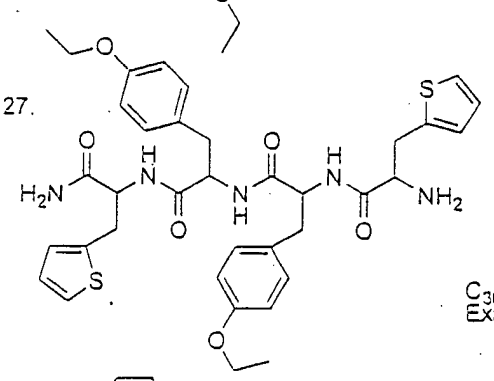
$C_{38}H_{44}ClN_5O_6S$
Exact Mass: 733.27

26.



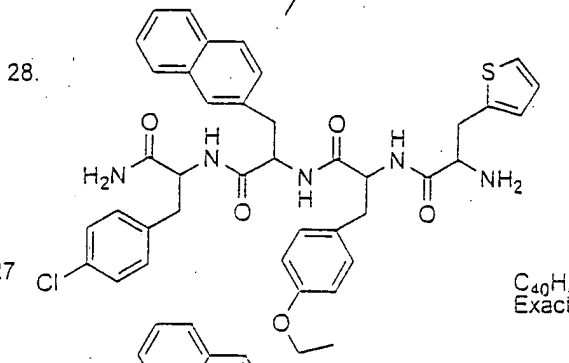
$C_{38}H_{44}N_6O$
Exact Mass

27.



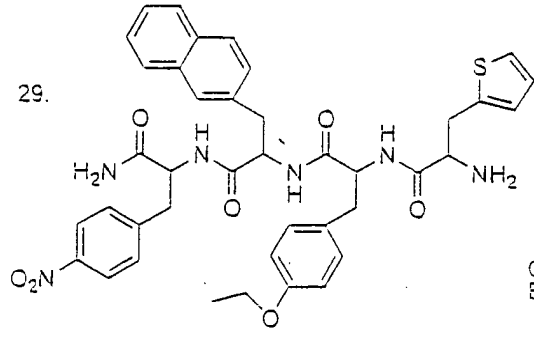
$C_{36}H_{43}N_5O_6S_2$
Exact Mass: 705.27

28.



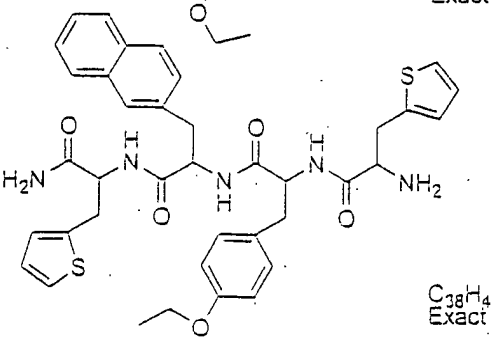
$C_{40}H_{42}ClN_5$
Exact Mass

29.



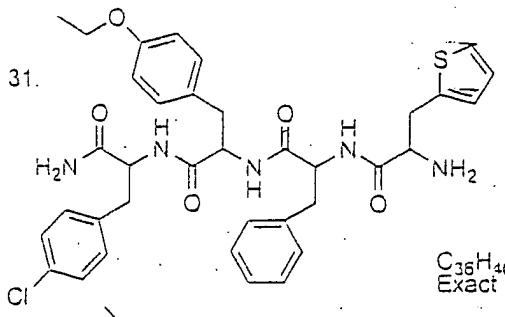
$C_{40}H_{42}N_6O_7S$
Exact Mass: 750.28

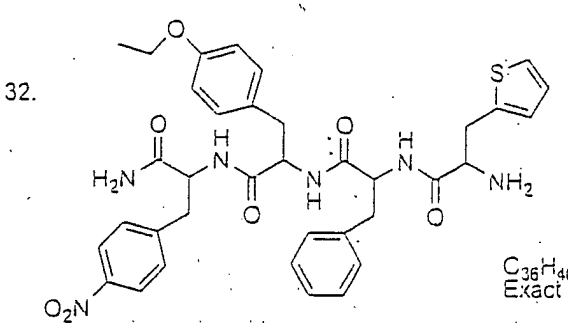
30.

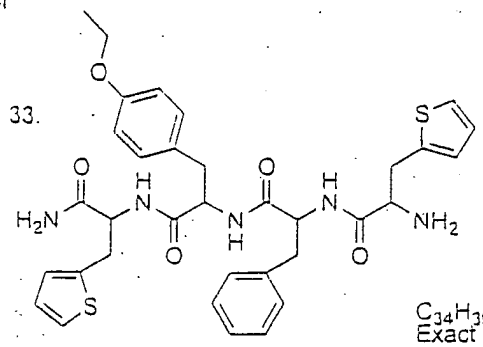


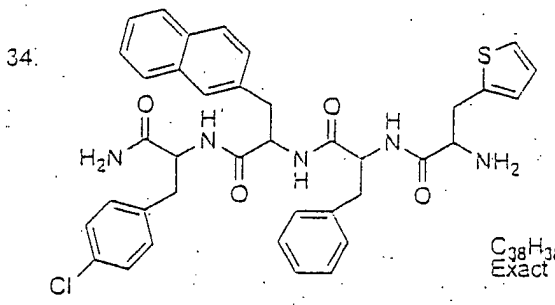
$C_{38}H_{41}N_5O$
Exact Mass

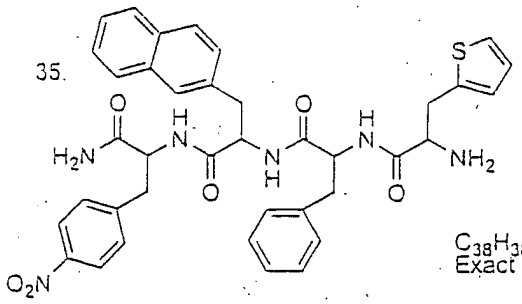
FIGURE 3C

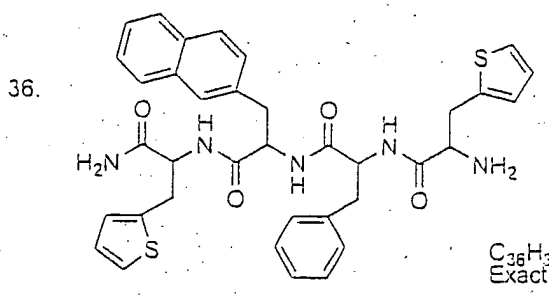

31.
$C_{36}H_{40}ClN_5O_5S$
Exact Mass: 689.24

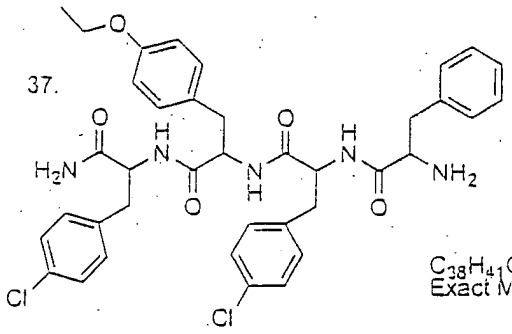

32.
$C_{36}H_{40}N_6O_7S$
Exact Mass: 7

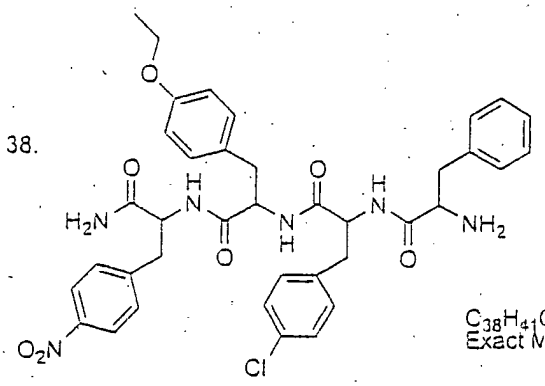

33.
$C_{34}H_{39}N_5O_5S_2$
Exact Mass: 661.24

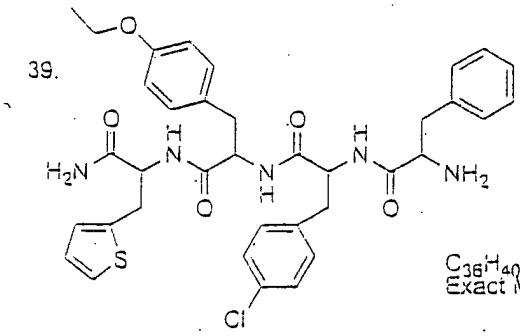

34.
$C_{38}H_{38}ClN_5O$
Exact Mass: 6


35.
$C_{38}H_{38}N_6O_6S$
Exact Mass: 706.26


36.
$C_{36}H_{37}N_5O_4S$
Exact Mass: 6


37.
$C_{38}H_{41}Cl_2N_5O_5$
Exact Mass: 717.25


38.
$C_{38}H_{41}ClN_6O_7$
Exact Mass: 72


39.
$C_{36}H_{40}ClN_5O_5S$
Exact Mass: 689.24

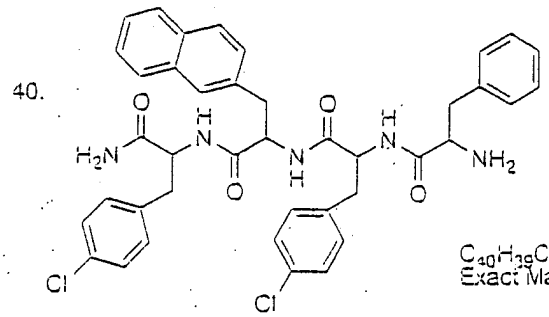
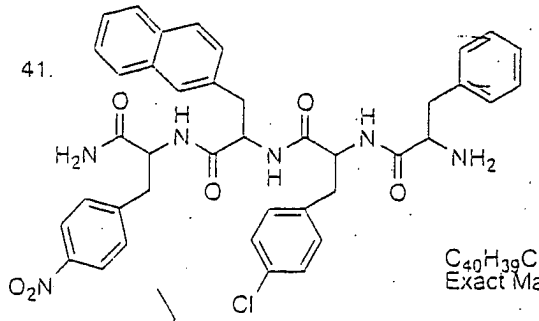

40.
$C_{40}H_{39}Cl_2N_5O_4$
Exact Mass: 72

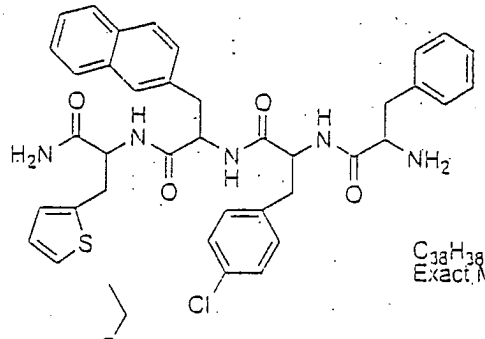
FIGURE 3D

41.



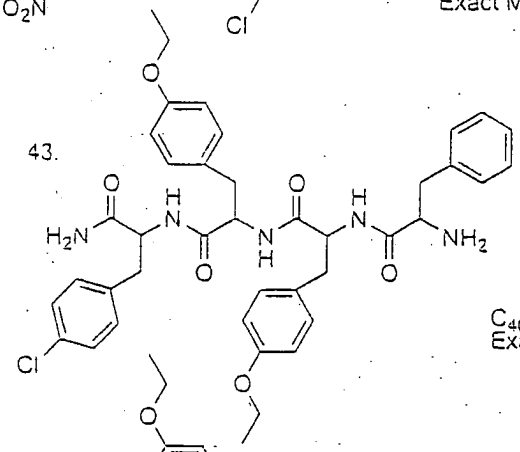
$C_{40}H_{39}ClN_6O_6$
Exact Mass: 734.26

42.



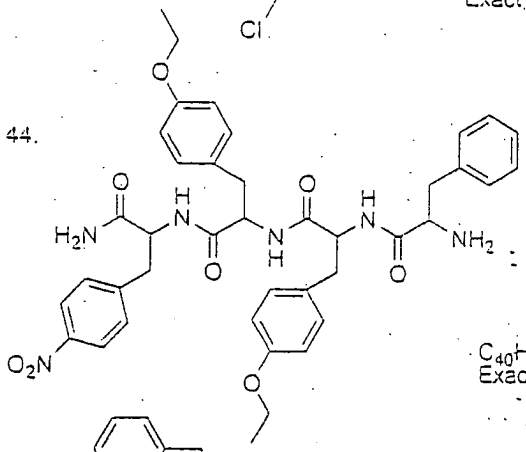
$C_{38}H_{38}ClN_5O$
Exact Mass:

43.



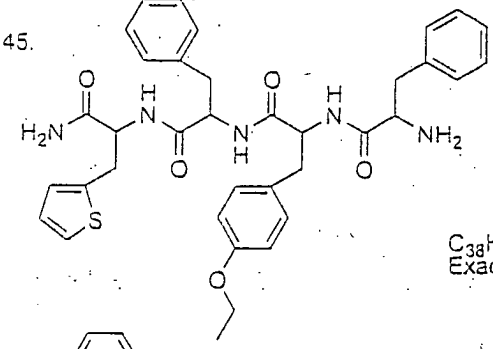
$C_{40}H_{46}ClN_5O_6$
Exact Mass: 727.31

44.



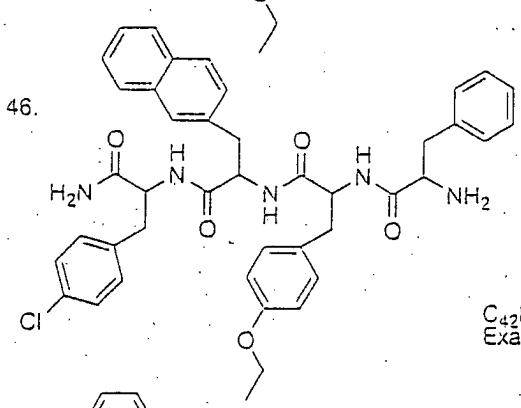
$C_{40}H_{46}N_6O_8$
Exact Mass:

45.



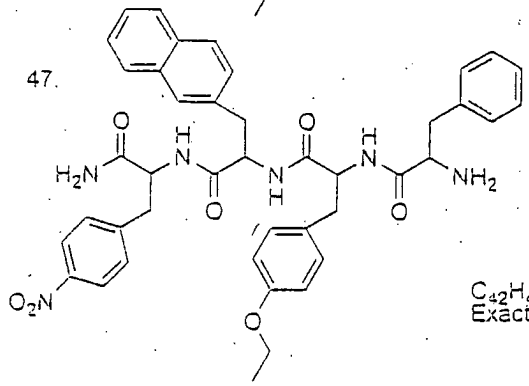
$C_{38}H_{45}N_5O_6S$
Exact Mass: 699.31

46.



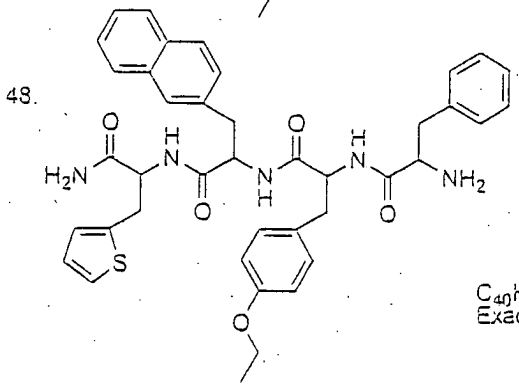
$C_{42}H_{44}ClN_5$
Exact Mass:

47.



$C_{42}H_{44}N_6O_7$
Exact Mass: 744.33

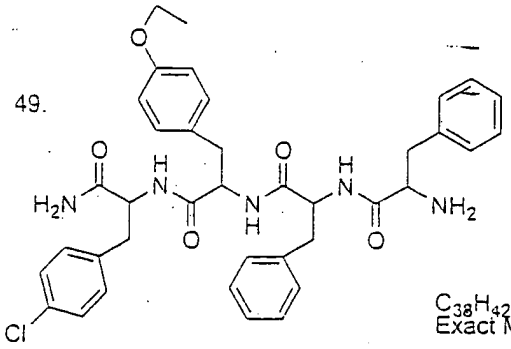
48.



$C_{40}H_{43}N_5O_5S$
Exact Mass:

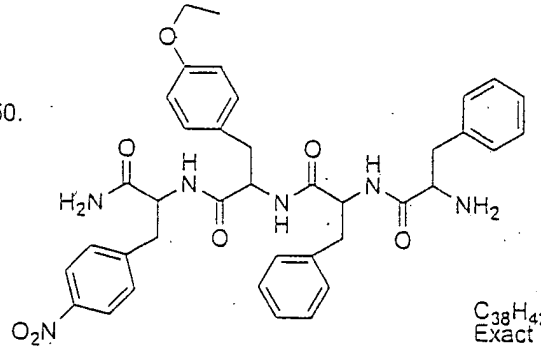
FIGURE 3E

49.



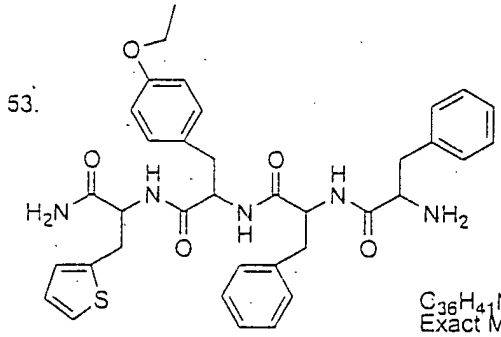
$C_{38}H_{42}ClN_5O5$
Exact Mass: 683.29

50.



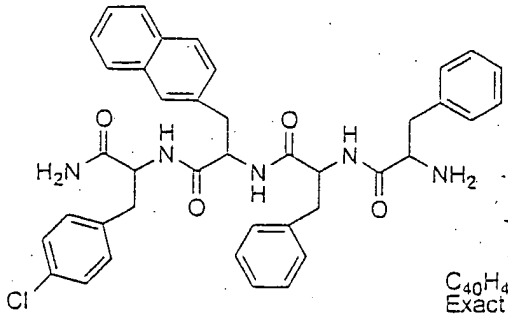
$C_{38}H_{42}N_5O_7$
Exact Mass: 6

53.



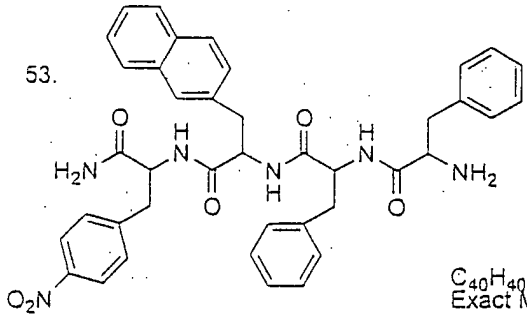
$C_{36}H_{41}N_5O_5S$
Exact Mass: 655.28

52.



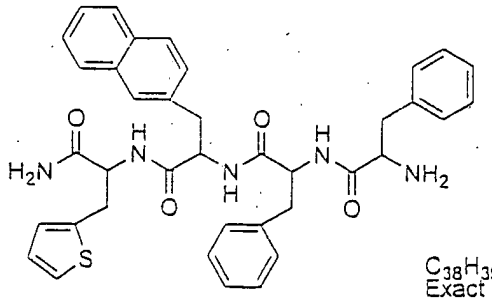
$C_{40}H_{40}ClN_5O$
Exact Mass: 6

53.



$C_{40}H_{40}N_6O_6$
Exact Mass: 700.30

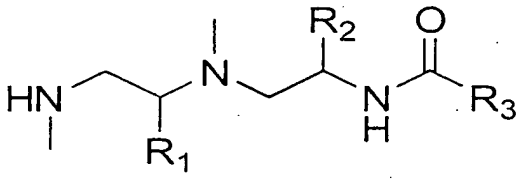
54.



$C_{38}H_{39}N_5O_4S$
Exact Mass: 6

FIGURE 3F

Define functionalities of most active mixtures of N-Acyl triamine library (TPI 914)



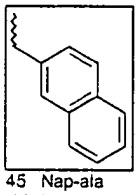
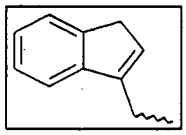
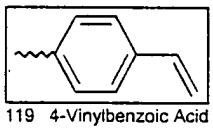
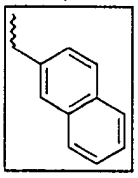
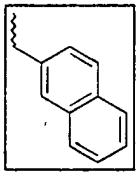
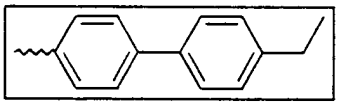
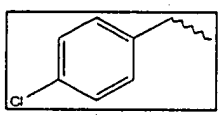
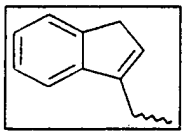
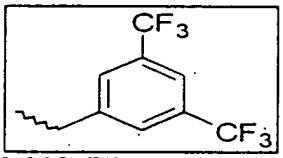
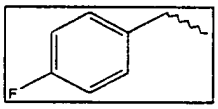
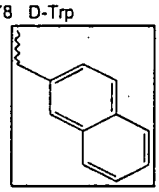
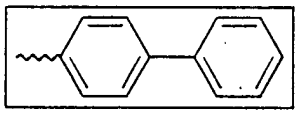
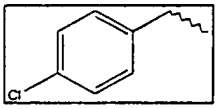
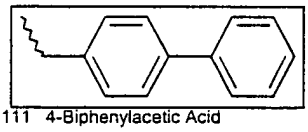
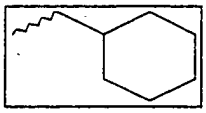
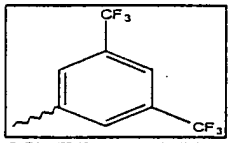
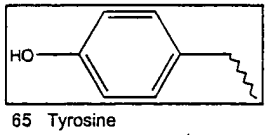
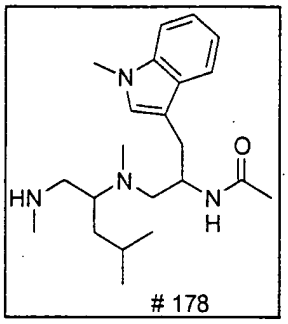
R1	R2	R3
 45 Nap-ala	 64 L-Trp(CHO)	 119 4-Vinylbenzoic Acid
 46 Nap-Ala	 96 Nap-Ala	 135 4-Ethyl-4-Biphenylcarboxylic Acid
 47 4-Chloro-phenylalanine	 78 D-Trp	 110 3,5-Bis(Triflouromethyl)-phenylacetic Acid
 48 4-Fluoro-phenylalanine	 95 Nap-ala	 139 4-Biphenylcarboxylic Acid
	 97 4-Chloro-phenylalanine	 111 4-Biphenylacetic Acid
	 81 D-cyclohexylalanine	 128 3,5-Bis-(Trifruoromethyl)-benzoic Acid
	 65 Tyrosine	

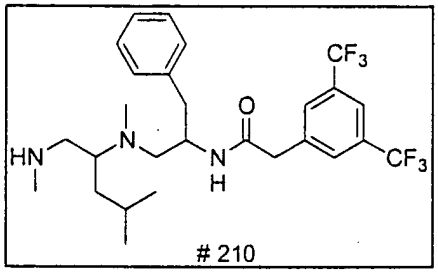
FIGURE 4

TPI 914 Controls

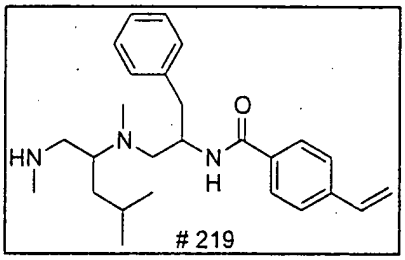
#	R1	R2	R3	Lowest concentration with Ratio of ~ 2.0
178	L-Leu	D-Trp	CH3	12.5 ug/ml
210	L-Leu	L-Phe	3,5-Bis(Trifluoromethyl)-Phenylacetic Acid	6.25 ug/ml
219	L-Leu	L-Phe	4-Vinylbenzoic Acid	6.25 ug/ml
235	L-Leu	L-Phe	4-Ethyl-4-Biphenylcarboxylic Acid	6.25 ug/ml



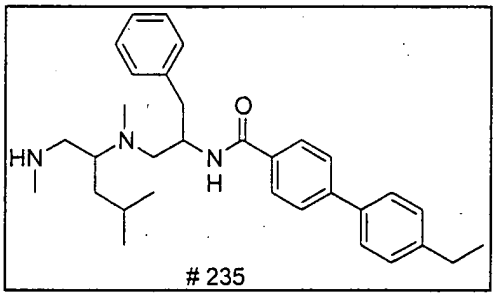
178



210



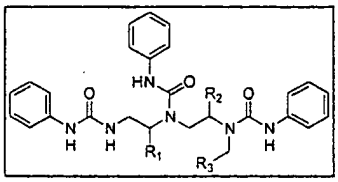
219



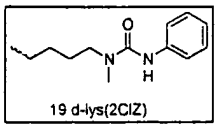
235

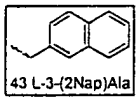
FIGURE 5

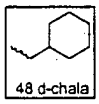
TPI 927

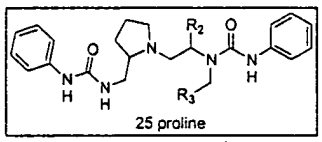


R1

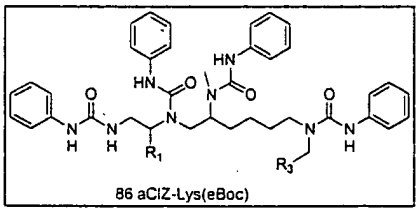


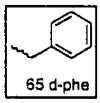


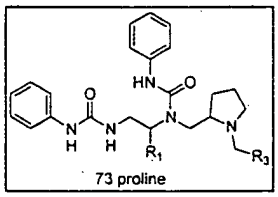


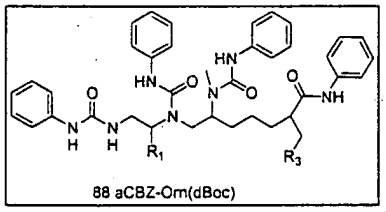


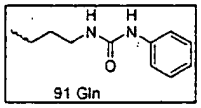
R2

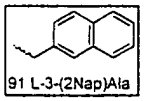


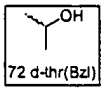




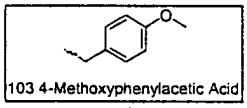


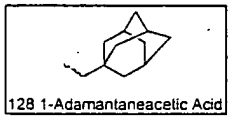


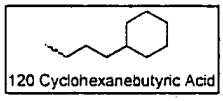


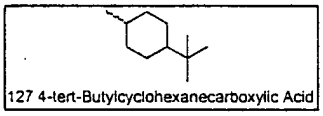


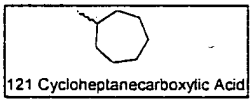
R3

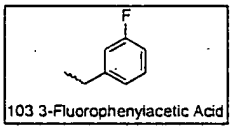


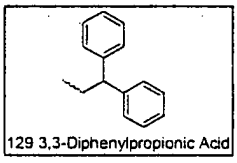


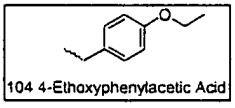


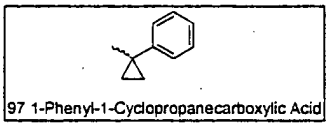












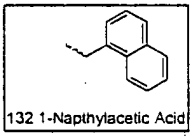


FIGURE 6

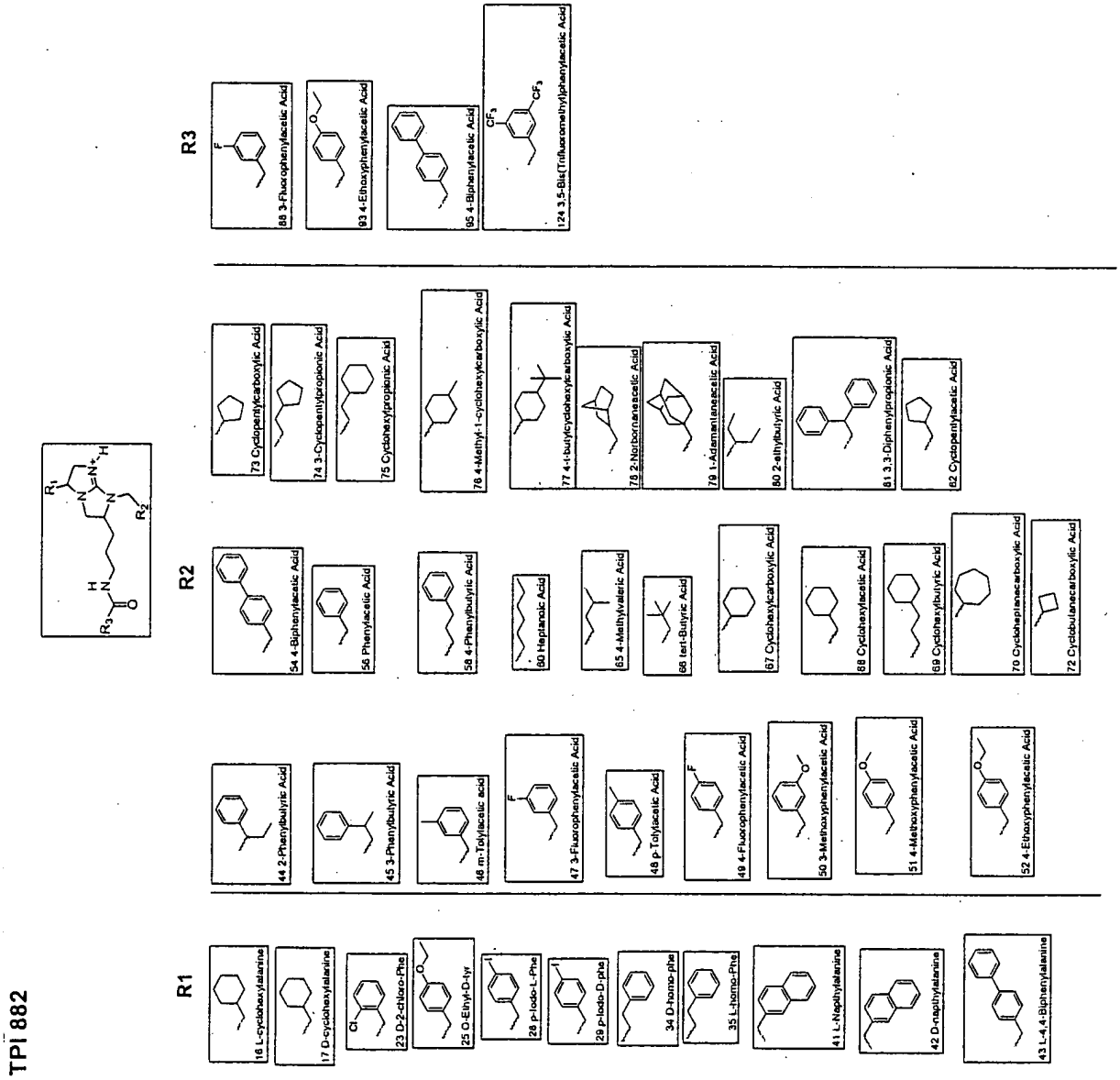
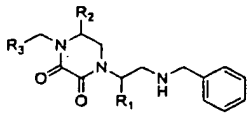

TPI 882
R1
16 L-cyclohexylalanine
17 D-cyclohexylalanine
23 D-2-chloro-Phe
25 O-Ethyl-D-tyr
28 p-Iodo-L-Phe
29 p-Iodo-D-phe
34 D-homo-phe
35 L-homo-Phe
41 L-Napthylalanine
42 D-napthylalanine
43 L-4,4-Biphenylalanine
R2
44 2-Phenylbutyric Acid
45 3-Phenylbutyric Acid
46 m-Tolylacetic acid
47 3-Fluorophenylacetic Acid
48 p-Tolylacetic Acid
49 4-Fluorophenylacetic Acid
50 3-Methoxyphenylacetic Acid
51 4-Methoxyphenylacetic Acid
52 4-Ethoxyphenylacetic Acid
54 4-Biphenylacetic Acid
56 Phenylacetic Acid
58 4-Phenylbutyric Acid
60 Heptanoic Acid
65 4-Methylvaleric Acid
66 tert-Butyric Acid
67 Cyclohexylcarboxylic Acid
68 Cyclohexylacetic Acid
69 Cyclohexylbutyric Acid
70 Cycloheptanecarboxylic Acid
72 Cyclobutanecarboxylic Acid
73 Cyclopentylcarboxylic Acid
74 3-Cyclopentylpropionic Acid
75 Cyclohexylpropionic Acid
76 4-Methyl-1-cyclohexylcarboxylic Acid
77 4-t-butylcyclohexylcarboxylic Acid
78 2-Norbornaneacetic Acid
79 1-Adamantaneacetic Acid
80 2-ethylbutyric Acid
81 3,3-Diphenylpropionic Acid
82 Cyclopentylacetic Acid
R3
88 3-Fluorophenylacetic Acid
93 4-Ethoxyphenylacetic Acid
95 4-Biphenylacetic Acid
124 3,5-Bis(Trifluoromethyl)phenylacetic Acid

FIGURE 7

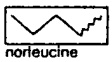
TPI 759 N-Benzyl-1,4,5-trisubstited-2,3-diketopiperazines

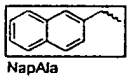


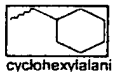
Selections	R1		R2		R3	
	21	Fmoc-Nle	43	Fmoc-leu	65	4-Isobutyl-alpha-Methylphenylacetic Acid
	22	Fmoc-nle	52	Fmoc-NapAl	67	3,5-Bis(Trifluoromethyl)-Phenylacetic Acid
	25	Fmoc-NapAla	41	Fmoc-phe	72	Heptanoic Acid
	29	Fmoc-chala	31	Fmoc-Phe	60	(Alpha-Alpha-Alpha-Trifluoro-m-Tolyl) acetic acid
	28	Fmoc-ChAla	42	Fmoc-ile	87	4-tert-Butyl-cyclohexanecarboxylic Acid
	5	Fmoc-Lys(Boc	33	Fmoc-Ile	58	m-Tolylacetic Acid
	24	Fmoc-nva	46	Fmoc-val	66	3,4-Dichlorophenylacetic Acid
	23	Fmoc-Nva	34	Fmoc-Leu	89	3,3-Diphenyl propionic Acid
	19	Fmoc-val			90	Dicyclohexylacetic acid
					81	Cycloheptanecarboxylic Acid
					61	p-Tolylacetic Acid
					80	Cyclohexanebutyric Acid

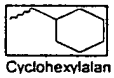
R1

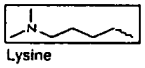

21 Norleucine


22 norleucine


25 NapAla


29 cyclohexylalani


28 Cyclohexylalan

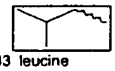

5 Lysine

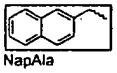

24 norvaline


23 Norvaline


19 valine

R2

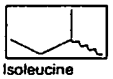

43 leucine


52 NapAla

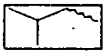

41 phenylalan


31 Phenylalar

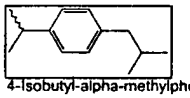

42 isoleucine

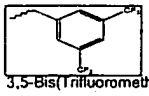

33 Isoleucine

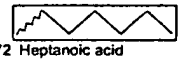

46 valine

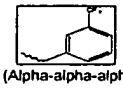

34 Leucine

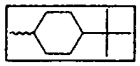
R3

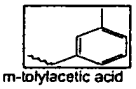

65 4-Isobutyl-alpha-methylphenylacetic acid

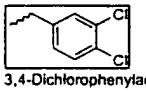

67 3,5-Bis(Trifluoromethyl)-phenylacetic acid

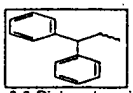

72 Heptanoic acid

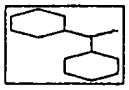

60 (Alpha-alpha-alpha-trifluoro-m-tolyl)acetic acid

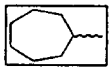

87 4-tert-Butyl-cyclohexanecarboxylic acid

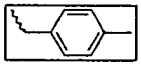

58 m-tolylacetic acid


66 3,4-Dichlorophenylacetic acid


89 3,3-Diphenylpropionic acid


90 Dicyclohexylacetic acid


81 Cycloheptanecarboxylic acid


61 p-Tolylacetic acid

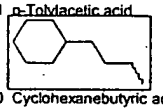
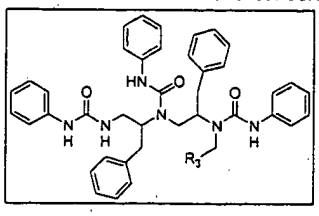
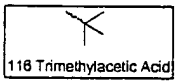

80 Cyclohexanebutyric acid

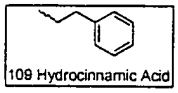
FIGURE 8

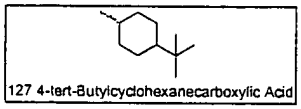
TPI 927 controls
Most of the compounds shown below can be considered active at 25 ug/ml

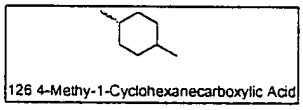


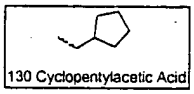
R3

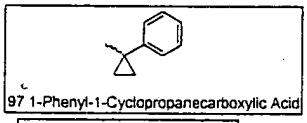

116 Trimethylacetic Acid

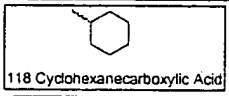

109 Hydrocinnamic Acid

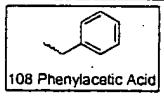

127 4-tert-Butylcyclohexanecarboxylic Acid

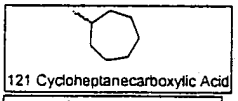

126 4-Methy-1-Cyclohexanecarboxylic Acid

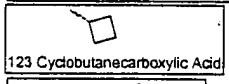

130 Cyclopentylacetic Acid

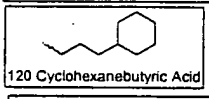

97 1-Phenyl-1-Cyclopropanecarboxylic Acid

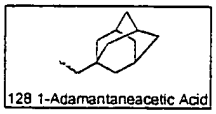

118 Cyclohexanecarboxylic Acid

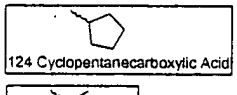

108 Phenylacetic Acid


121 Cycloheptanecarboxylic Acid

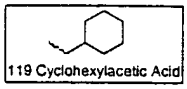

123 Cyclobutanecarboxylic Acid

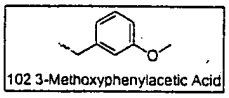

120 Cyclohexanebutyric Acid


128 1-Adamantaneacetic Acid

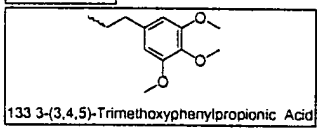

124 Cyclopentanecarboxylic Acid


113 Isobutyric Acid

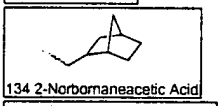

119 Cyclohexylacetic Acid

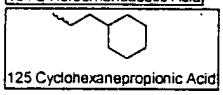

102 3-Methoxyphenylacetic Acid


111 Butyric Acid

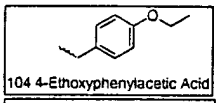

133 3-(3,4,5)-Trimethoxyphenylpropionic Acid

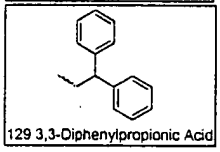

112 Heptanoic Acid

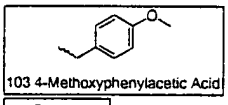

134 2-Norbornaneacetic Acid

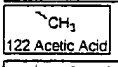

125 Cyclohexanepropionic Acid

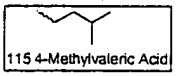

117 tert-Butyl acetic Acid

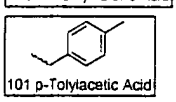

104 4-Ethoxyphenylacetic Acid


129 3,3-Diphenylpropionic Acid


103 4-Methoxyphenylacetic Acid


122 Acetic Acid


115 4-Methylvaleric Acid


101 p-Tolylacetic Acid

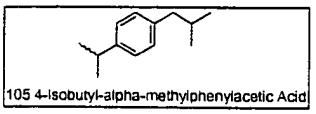
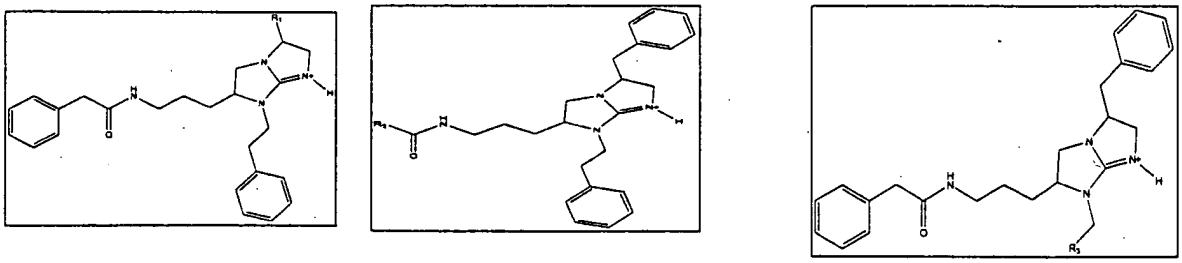

105 4-Isobutyl-alpha-methylphenylacetic Acid

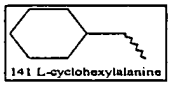
FIGURE 9

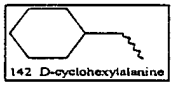
TPI 882 controls

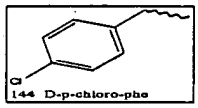
All the compounds below have activity at 8 ug/ml

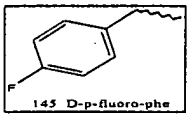


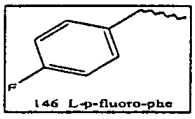
R1

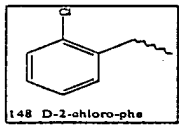

141 L-cyclohexylalanine

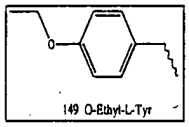

142 D-cyclohexylalanine

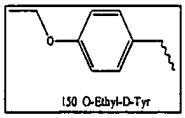

144 D-p-chloro-phe

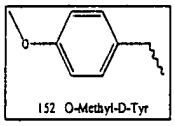

145 D-p-fluoro-phe

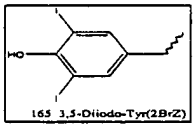

146 L-p-fluoro-phe

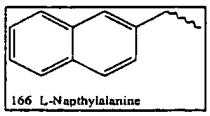

148 D-2-chloro-phe


149 O-Ethyl-L-Tyr

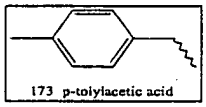

150 O-Ethyl-D-Tyr

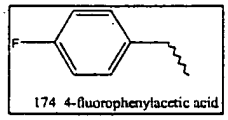

152 O-Methyl-D-Tyr

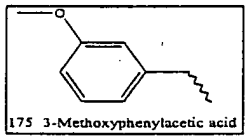

165 3,5-Diodo-Tyr(2BrZ)

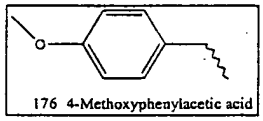

166 L-Napthylalanine

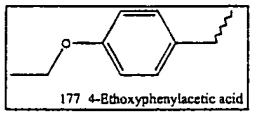
R2

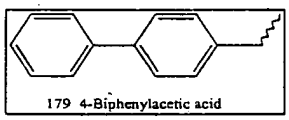

173 p-toiylacetic acid

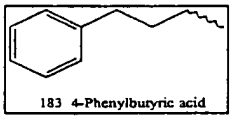

174 4-fluorophenylacetic acid


175 3-Methoxyphenylacetic acid

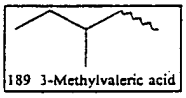

176 4-Methoxyphenylacetic acid

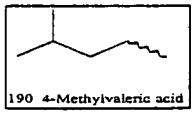

177 4-Ethoxyphenylacetic acid


179 4-Biphenylacetic acid

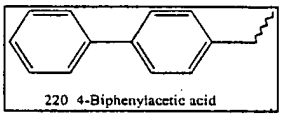

183 4-Phenylbutyric acid

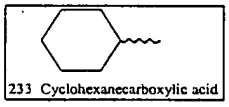

185 Heptanoic acid

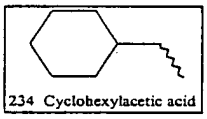

189 3-Methylvaleric acid

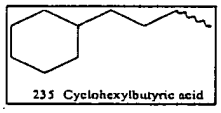

190 4-Methylvaleric acid

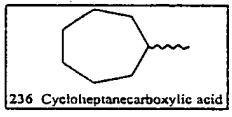
R3

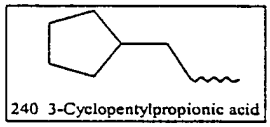

220 4-Biphenylacetic acid

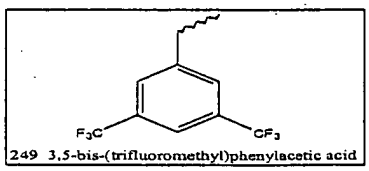

233 Cyclohexanecarboxylic acid


234 Cyclohexylacetic acid


235 Cyclohexylbutyric acid


236 Cycloheptanecarboxylic acid


240 3-Cyclopentylpropionic acid



249 3,5-bis-(trifluoromethyl)phenylacetic acid

FIGURE 10

Hexape~1 TPI1239 dose responses (sort)

TPI 1239 All mix are N-terminal free and C-terminal amide

Caspase 3-XIAP

From file 032001-IC50 of selected TPI 1239

Note that Smac is only tested at 1 mM

Caspase effect

	2 ug/ml		1ug/ml		0.5 ug/ml		0.25 ug/ml	
	Avg	std	Avg	std	Avg	std	Avg	std
Caspase 3	1.0	0.0	1.0	0.0	1.0	0.0	1.0	0.0
Xiap+C3	0.4	0.0	0.4	0.0	0.4	0.0	0.4	0.0
SMAC	0.9	0.1	0.9	0.1	0.9	0.1	0.9	0.1
XXXAWW	1.0	0.0	1.1	0.0	1.1	0.0	1.0	0.0
XXXHWW	1.0	0.1	1.1	0.0	1.1	0.0	1.0	0.1
XXXKWW	1.0	0.1	1.0	0.0	1.0	0.0	1.1	0.1
XXXNWW	1.0	0.0	1.0	0.0	1.0	0.0	1.0	0.0
XXXQWW	1.0	0.0	1.0	0.0	1.0	0.0	1.0	0.0
XXXRWW	1.0	0.0	1.0	0.0	1.0	0.0	1.0	0.0
XXXSWW	1.0	0.0	1.0	0.0	1.0	0.0	1.0	0.1
XXXTWW	1.1	0.0	1.1	0.0	1.1	0.0	1.0	0.0
XXXVWW	1.0	0.0	0.9	0.0	1.0	0.1	1.0	0.0
XXXXWW	1.0	0.0	1.1	0.1	1.0	0.0	1.1	0.0

XIAP effect

	2ug/ml	Std	1ug/ml	Std	0.5 ug/ml	Std	0.25 ug/ml	Std
Caspase 3	2.2	0.0	2.2	0.0	2.2	0.0	2.2	0.0
Xiap+C3	1.0	0.0	1.0	0.0	1.0	0.0	1.0	0.0
SMAC	2.0	0.1	2.0	0.1	2.0	0.1	2.0	0.1
XXXAWW	2.2	0.0	2.0	0.0	1.7	0.0	1.4	0.0
XXXKWW	2.2	0.1	2.0	0.2	1.6	0.1	1.2	0.1
XXXTWW	2.1	0.0	1.8	0.0	1.6	0.0	1.2	0.1
XXXSWW	2.1	0.2	1.8	0.0	1.4	0.1	1.3	0.3
XXXNWW	1.8	0.2	1.4	0.0	1.2	0.1	1.1	0.1
XXXVWW	1.7	0.0	1.4	0.0	1.2	0.2	1.0	0.1
XXXXWW	1.8	0.1	1.4	0.1	1.1	0.1	1.1	0.3
XXXHWW	1.8	0.1	1.4	0.1	1.1	0.1	1.0	0.1
XXXRWW	1.4	0.1	1.1	0.0	1.1	0.1	0.9	0.1
XXXQWW	1.5	0.0	1.3	0.0	1.1	0.1	0.9	0.1

Analysis:

-No effect on caspase activity, first block of data.

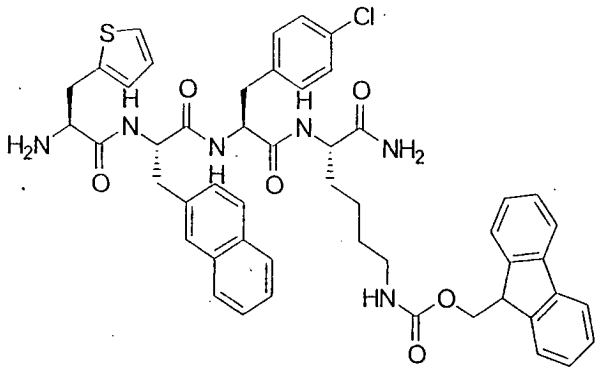
-The most active mixtures from XXXOWW are A, K and T

- The next step of the deconvolution could be a PS-SCL for positions 1,2 and 3, position 4 having A,K,T and positions 5 and 6 as W

FIGURE 11

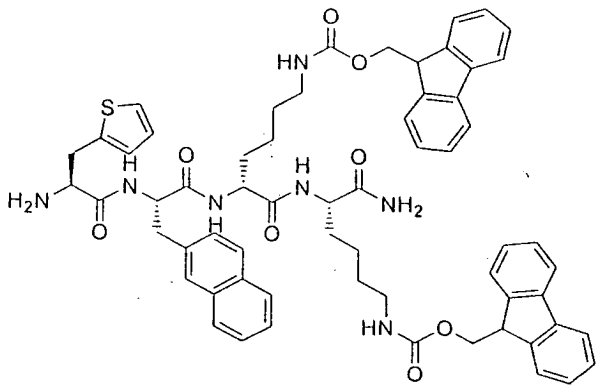
Tetra-peptide antagonists of XIAP

792-33



Exact Mass: 898.32793

792-35



Exact Mass: 1067.46153

FIGURE 12

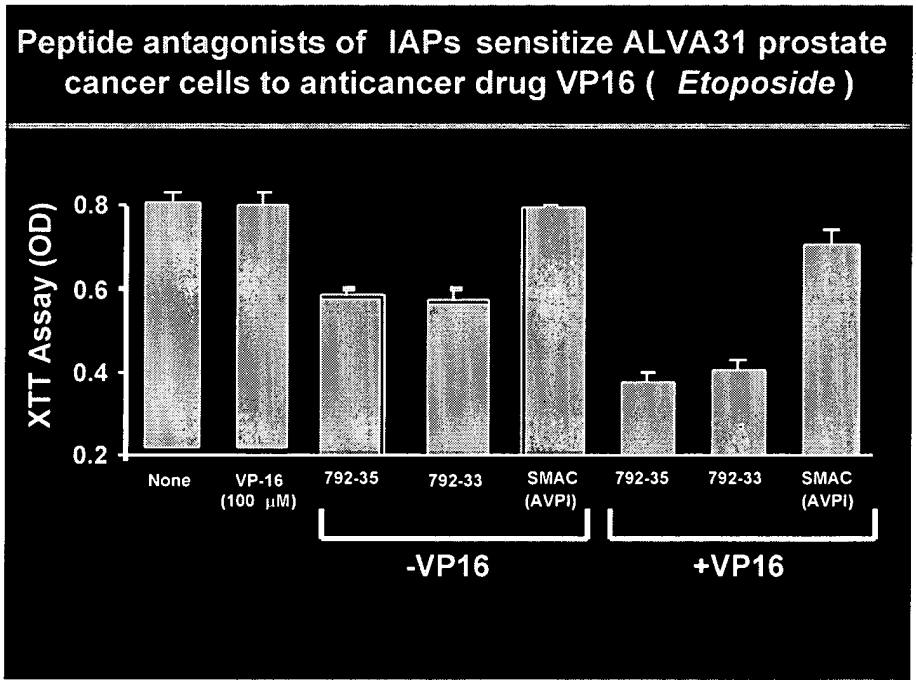
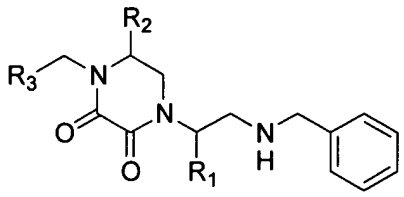

Peptide antagonists of IAPs sensitize ALVA31 prostate cancer cells to anticancer drug VP16 (Etoposide)
XTT Assay (OD)
0.8
0.6
0.4
0.2
None
VP-16 (100 μM)
792-35
792-33
SMAC (AVPI)
792-35
792-33
SMAC (AVPI)
-VP16
+VP16

FIGURE 13

TPI 1391
N-Benzyl-1,4,5-trisubstited-2,3-diketopiperazines



TPI 1396
Polyphenylureas
Diphenyl or Triphenylureas

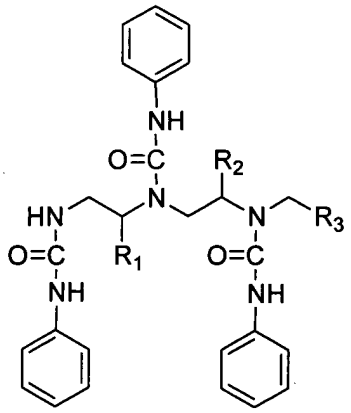
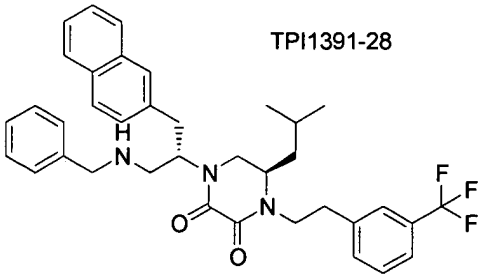


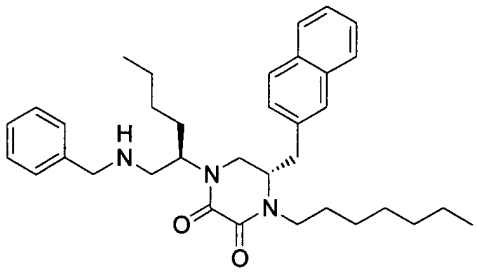
FIGURE 14A

TPI1391-28



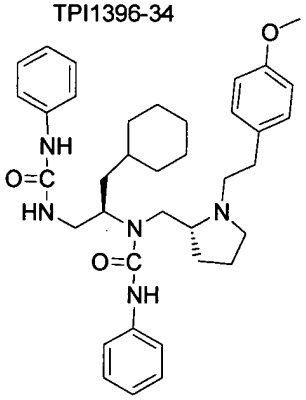
Exact Mass: 615.31

TPI1391-21



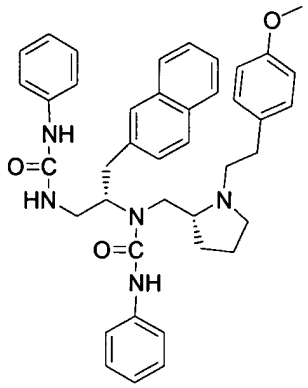
Exact Mass: 541.37

TPI1396-34



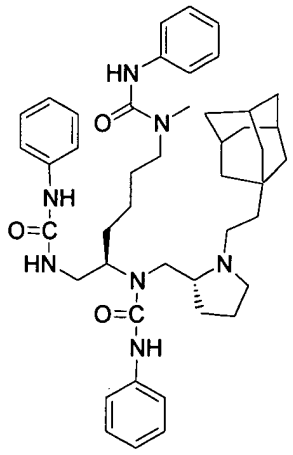
Exact Mass: 611.38

TPI1396-22



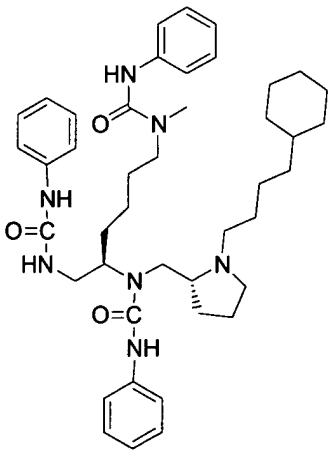
Exact Mass: 655.35

TPI1396-11



Exact Mass: 747.48

TPI1396-12



Exact Mass: 723.48

FIGURE 14B

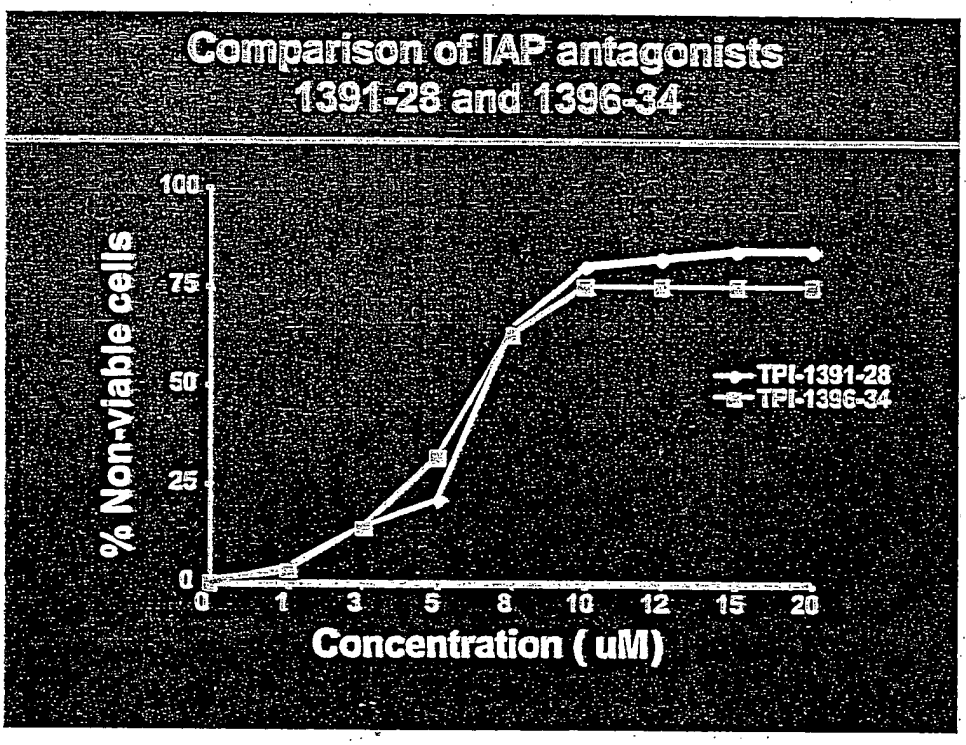

Comparison of IAP antagonists
1391-28 and 1396-34
% Non-viable cells
100
75
50
25
0
0
1
3
5
8
10
12
15
20
Concentration (uM)
TPI-1391-28
TPI-1396-34

FIGURE 15

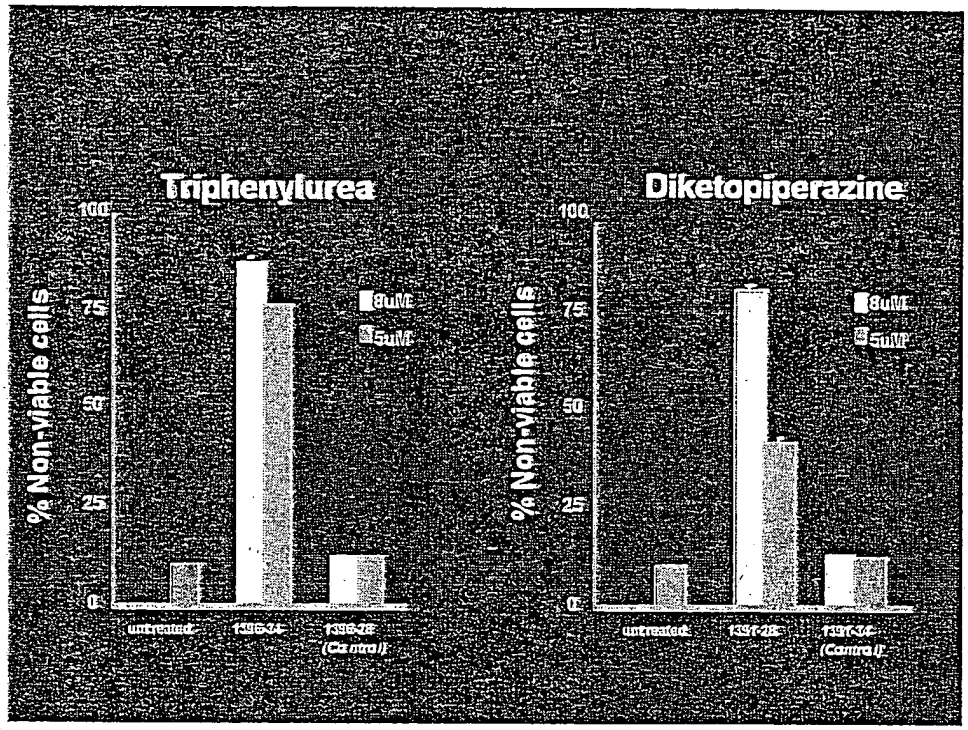

Triphenylurea
Diketopiperazine
% Non-viable cells
100
75
50
25
0
8uM
5uM
untreated
1396-44
1396-28
(Camra)
1396-28

FIGURE 16

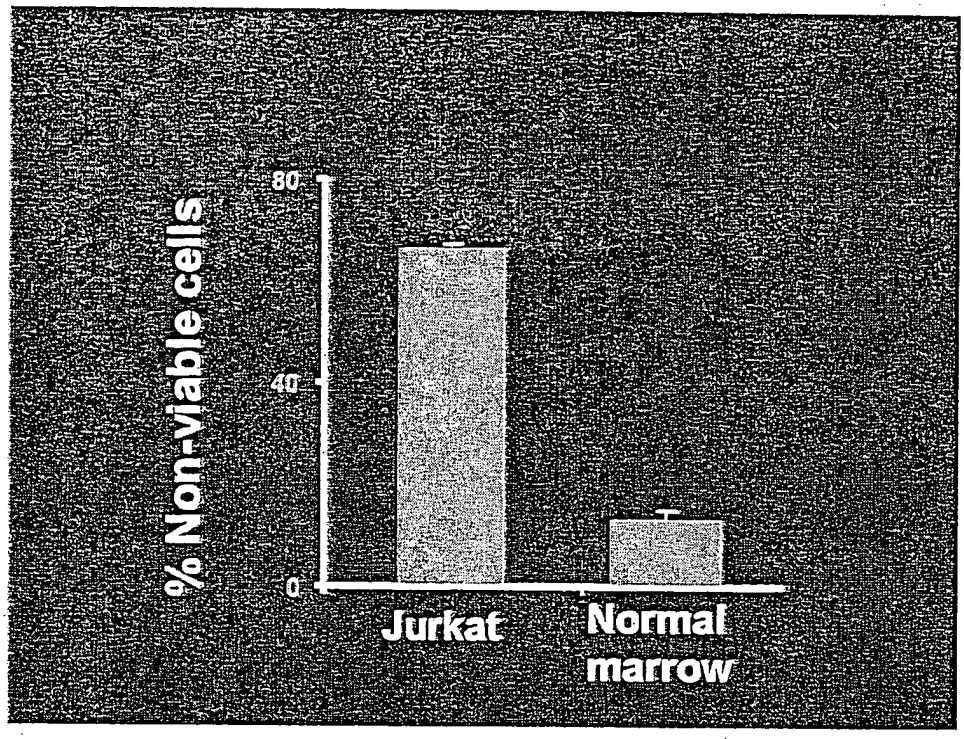


FIGURE 17

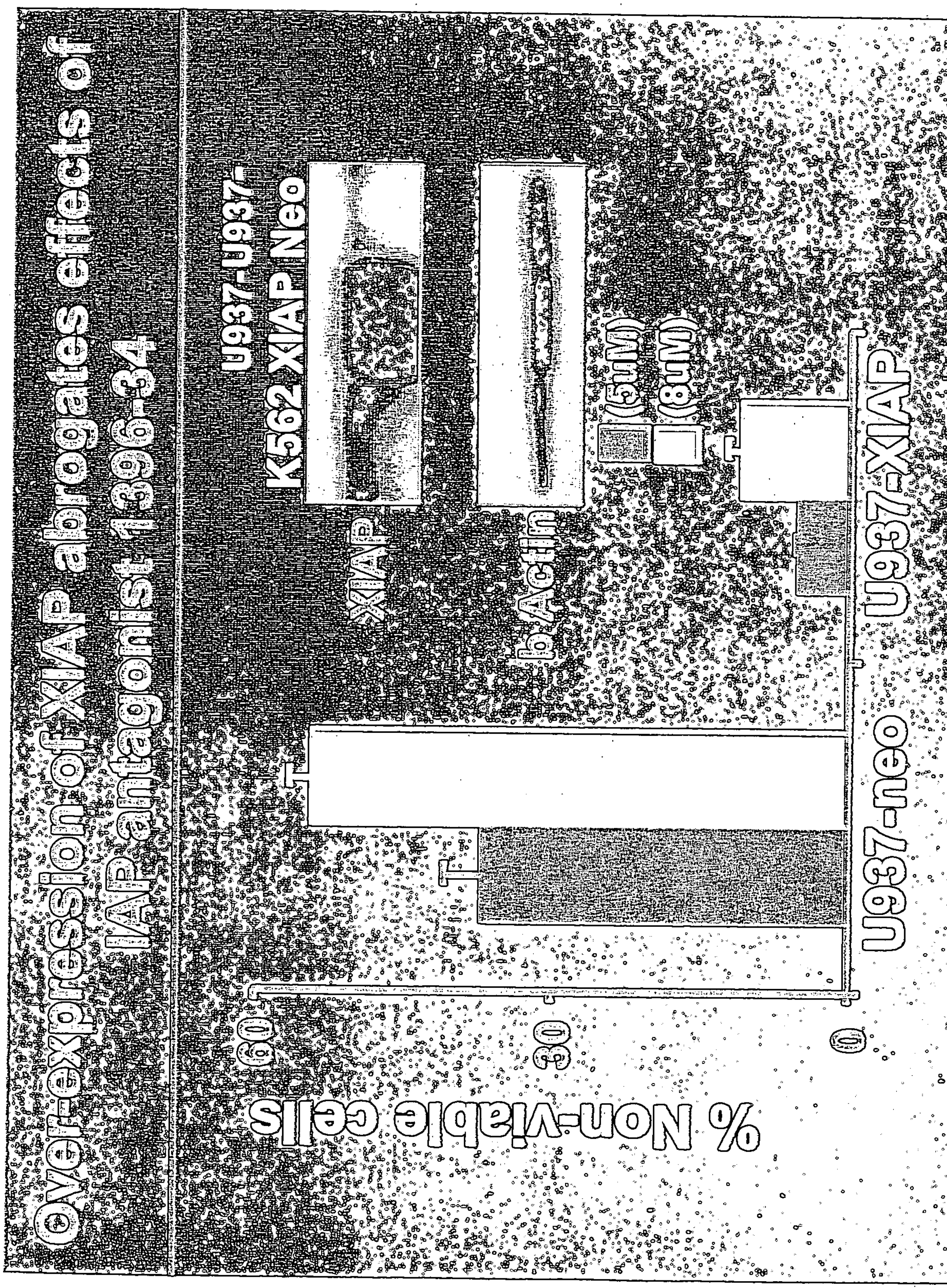

Over-expression of XIAP abrogates effects of IAP antagonist 1396-34
U937-U937-
K562 XIAP Neo
XIAP
Actin
(5uM)
(8uM)
% Non-viable cells
60
30
0
U937-neo
U937-XIAP

FIGURE 18

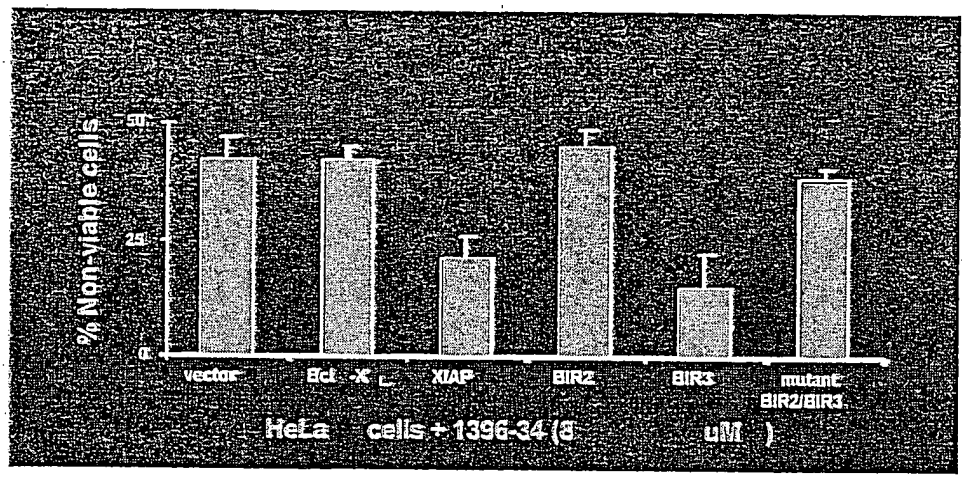
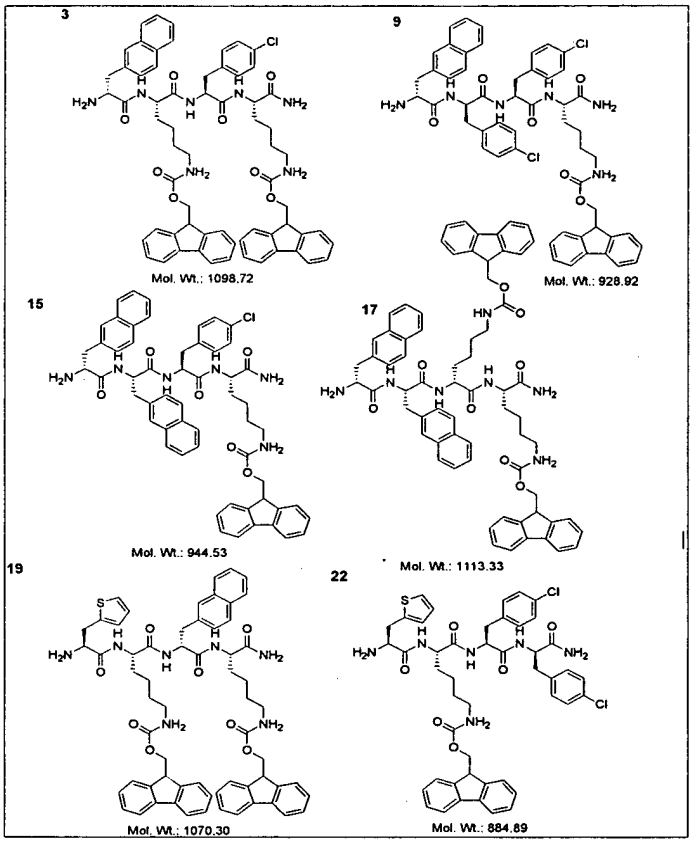

% Non-viable cells
vector
Bcl-X
XIAP
BIR2
BIR3
mutant BIR2/BIR3
HeLa cells + 1396-34 (
uM)

FIGURE 19


3
Mol. Wt.: 1098.72
9
Mol. Wt.: 928.92
15
Mol. Wt.: 944.53
17
Mol. Wt.: 1113.33
19
Mol. Wt.: 1070.30
22
Mol. Wt.: 884.89

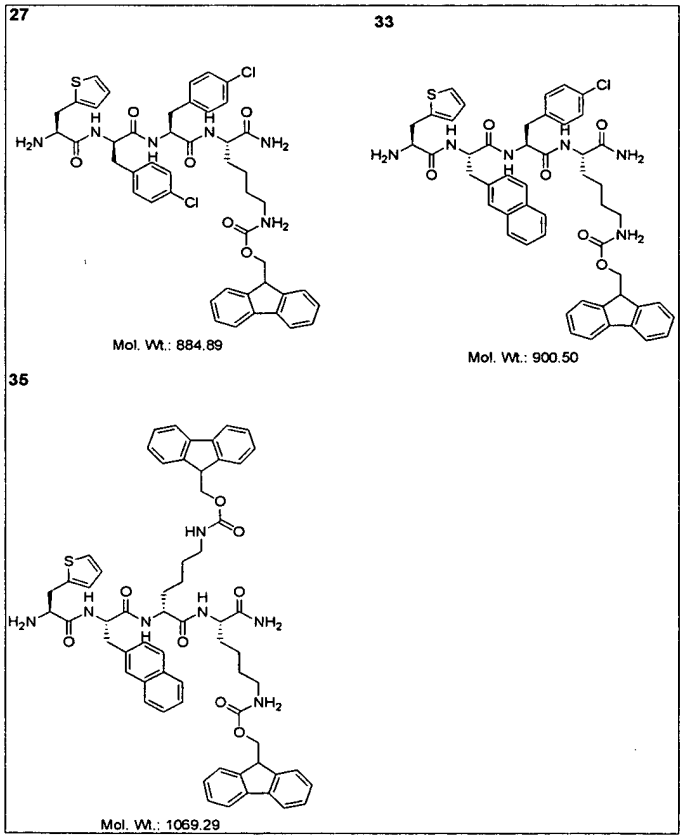

27
Mol. Wt.: 884.89
33
Mol. Wt.: 900.50
35
Mol. Wt.: 1069.29

FIGURE 20

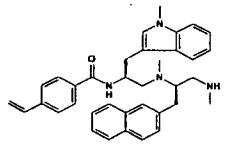
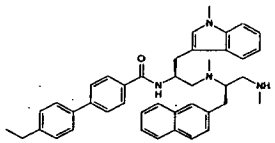
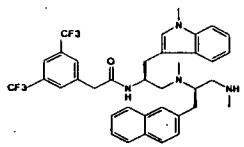
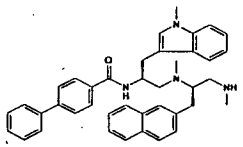
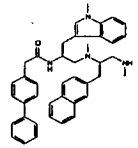
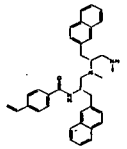
TPI1349	Structures FIGURE 21	MW	Exact Mass	Name	MLogP	HBondAcceptor	HBondDonor	RuleOfFive
1	 [Boc-D-(2-Naphthyl)-alanine][Boc-L-Tryptophan(Formyl)][4-Vinylbenzoic acid]	544.7	544.3	N-[(1S)-2-(1-methyl-1H-indol-3-yl)-1-({methyl[(1R)-2-(methylamino)-1-(2-naphthylmethyl)ethyl]amino}methyl)ethyl]-4-vinylbenzamide	4.3	5	2	2
2	 [Boc-D-(2-Naphthyl)-alanine][Boc-L-Tryptophan(Formyl)][4-Ethyl-4-Biphenylcarboxylic acid]	622.9	622.4	4'-ethyl-N-[(1S)-2-(1-methyl-1H-indol-3-yl)-1-({methyl[(1R)-2-(methylamino)-1-(2-naphthylmethyl)ethyl]amino}methyl)ethyl]-1,1'-biphenyl-4-carboxamide	5.2	5	2	2
3	 [Boc-D-(2-Naphthyl)-alanine][Boc-L-Tryptophan(Formyl)][3,5-Bis-(trifluoromethyl)-phenylacetic acid]	668.7	668.3	2-[3,5-bis(trifluoromethyl)phenyl]-N-[(1S)-2-(1-methyl-1H-indol-3-yl)-1-({methyl[(1R)-2-(methylamino)-1-(2-naphthylmethyl)ethyl]amino}methyl)ethyl]acetamide	5.6	5	2	2
4	 [Boc-D-(2-Naphthyl)-alanine][Boc-L-Tryptophan(Formyl)][4-Biphenylcarboxylic acid]	594.8	594.3	N-[(1S)-2-(1-methyl-1H-indol-3-yl)-1-({methyl[(1R)-2-(methylamino)-1-(2-naphthylmethyl)ethyl]amino}methyl)ethyl]-1,1'-biphenyl-4-carboxamide	4.9	5	2	2
5	 [Boc-D-(2-Naphthyl)-alanine][Boc-L-Tryptophan(Formyl)][4-Biphenylacetic acid]	608.8	608.4	2-(1,1'-biphenyl-4-yl)-N-[(1S)-2-(1-methyl-1H-indol-3-yl)-1-({methyl[(1R)-2-(methylamino)-1-(2-naphthylmethyl)ethyl]amino}methyl)ethyl]acetamide	4.8	5	2	2
6	 [Boc-D-(2-Naphthyl)-alanine][Boc-L-(2-Naphthyl)-alanine][4-Vinylbenzoic acid]	541.7	541.3	N-[(1S)-2-{methyl[(1R)-2-(methylamino)-1-(2-naphthylmethyl)ethyl]amino}-1-(2-naphthylmethyl)ethyl]-4-vinylbenzamide	5.6	4	2	2

FIGURE 21A

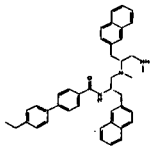
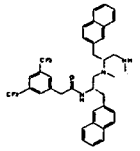
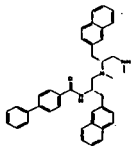
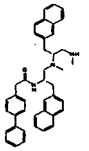
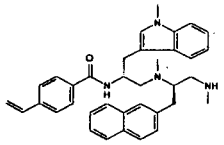
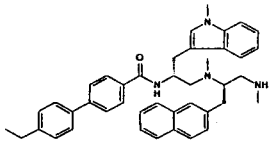
TPI1349	Structures FIGURE 21	MW	Exact Mass	Name	MLogP	HBondAcceptor	HBondDonor	RuleOfFive
7	 [Boc-D-(2-Naphthyl)-alanine][Boc-L-(2-Naphthyl)-alanine][4-Ethyl-4-Biphenylcarboxylic acid]	619.9	619.4	4'-ethyl-N-[(1S)-2-{methyl[(1R)-2-(methylamino)-1-(2-naphthylmethyl)ethyl]amino}-1-(2-naphthylmethyl)ethyl]-1,1'-biphenyl-4-carboxamide	6.5	4	2	2
8	 [Boc-D-(2-Naphthyl)-alanine][Boc-L-(2-Naphthyl)-alanine][3,5-Bis-(trifluoromethyl)-phenylacetic acid]	665.7	665.3	2-[3,5-bis(trifluoromethyl)phenyl]-N-[(1S)-2-{methyl[(1R)-2-(methylamino)-1-(2-naphthylmethyl)ethyl]amino}-1-(2-naphthylmethyl)ethyl]acetamide	6.9	4	2	2
9	 [Boc-D-(2-Naphthyl)-alanine][Boc-L-(2-Naphthyl)-alanine][4-Biphenylcarboxylic acid]	591.8	591.3	N-[(1S)-2-{methyl[(1R)-2-(methylamino)-1-(2-naphthylmethyl)ethyl]amino}-1-(2-naphthylmethyl)ethyl]-1,1'-biphenyl-4-carboxamide	6.2	4	2	2
10	 [Boc-D-(2-Naphthyl)-alanine][Boc-L-(2-Naphthyl)-alanine][4-Biphenylacetic acid]	605.8	605.3	2-(1,1'-biphenyl-4-yl)-N-[(1S)-2-{methyl[(1R)-2-(methylamino)-1-(2-naphthylmethyl)ethyl]amino}-1-(2-naphthylmethyl)ethyl]acetamide	6.1	4	2	2
11	 [Boc-D-(2-Naphthyl)-alanine][Boc-D-Tryptophan][4-Vinylbenzoic acid]	544.7	544.3	N-[(1R)-2-(1-methyl-1H-indol-3-yl)-1-({methyl[(1R)-2-(methylamino)-1-(2-naphthylmethyl)ethyl]amino}methyl)ethyl]-4-vinylbenzamide	4.3	5	2	2
12	 [Boc-D-(2-Naphthyl)-alanine][Boc-D-Tryptophan][4-Ethyl-4-Biphenylcarboxylic acid]	622.9	622.4	4'-ethyl-N-[(1R)-2-(1-methyl-1H-indol-3-yl)-1-({methyl[(1R)-2-(methylamino)-1-(2-naphthylmethyl)ethyl]amino}methyl)ethyl]-1,1'-biphenyl-4-carboxamide	5.2	5	2	2

FIGURE 21A (cont.)

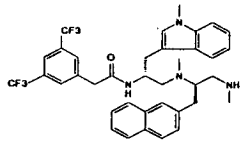
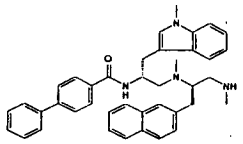
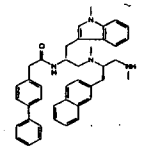
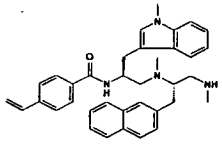
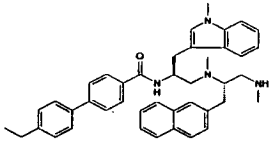
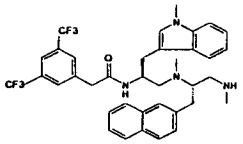
TPI1349	Structures FIGURE 21	MW	Exact Mass	Name	MLogP	HBondAcceptor	HBondDonor	RuleOfFive
13	 [Boc-D-(2-Naphthyl)-alanine][Boc-D-Tryptophan][3,5-Bis-(trifluoromethyl)-phenylacetic acid]	668.7	668.3	2-[3,5-bis(trifluoromethyl)phenyl]-N-[(1R)-2-(1-methyl-1H-indol-3-yl)-1-({methyl[(1R)-2-(methylamino)-1-(2-naphthylmethyl)ethyl]amino}methyl)ethyl]acetamide	5.6	5	2	2
14	 [Boc-D-(2-Naphthyl)-alanine][Boc-D-Tryptophan][4-Biphenylcarboxylic acid]	594.8	594.3	N-[(1R)-2-(1-methyl-1H-indol-3-yl)-1-({methyl[(1R)-2-(methylamino)-1-(2-naphthylmethyl)ethyl]amino}methyl)ethyl]-1,1'-biphenyl-4-carboxamide	4.9	5	2	2
15	 [Boc-D-(2-Naphthyl)-alanine][Boc-D-Tryptophan][4-Biphenylacetic acid]	608.8	608.4	2-(1,1'-biphenyl-4-yl)-N-[(1R)-2-(1-methyl-1H-indol-3-yl)-1-({methyl[(1R)-2-(methylamino)-1-(2-naphthylmethyl)ethyl]amino}methyl)ethyl]acetamide	4.8	5	2	2
16	 [Boc-L-(2-Naphthyl)-alanine][Boc-L-Tryptophan(Formyl)][4-Vinylbenzoic acid]	544.7	544.3	N-[(1S)-2-(1-methyl-1H-indol-3-yl)-1-({methyl[(1S)-2-(methylamino)-1-(2-naphthylmethyl)ethyl]amino}methyl)ethyl]-4-vinylbenzamide	4.3	5	2	2
17	 [Boc-L-(2-Naphthyl)-alanine][Boc-L-Tryptophan(Formyl)][4-Ethyl-4-Biphenylcarboxylic acid]	622.9	622.4	4'-ethyl-N-[(1S)-2-(1-methyl-1H-indol-3-yl)-1-({methyl[(1S)-2-(methylamino)-1-(2-naphthylmethyl)ethyl]amino}methyl)ethyl]-1,1'-biphenyl-4-carboxamide	5.2	5	2	2
18	 [Boc-L-(2-Naphthyl)-alanine][Boc-L-Tryptophan(Formyl)][3,5-Bis-(trifluoromethyl)-phenylacetic acid]	668.7	668.3	2-[3,5-bis(trifluoromethyl)phenyl]-N-[(1S)-2-(1-methyl-1H-indol-3-yl)-1-({methyl[(1S)-2-(methylamino)-1-(2-naphthylmethyl)ethyl]amino}methyl)ethyl]acetamide	5.6	5	2	2

FIGURE 21A (cont.)

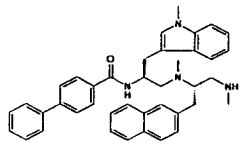
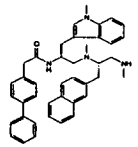
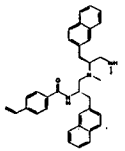
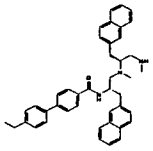
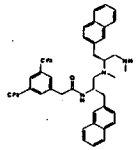
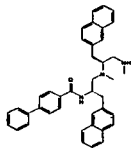
TPI1349	Structures FIGURE 21	MW	Exact Mass	Name	MLogP	HBondAcceptor	HBondDonor	RuleOfFive
19	 [Boc-L-(2-Naphthyl)-alanine][Boc-L-Tryptophan(Formyl)][4-Biphenylcarboxylic acid]	594.8	594.3	N-[(1S)-2-(1-methyl-1H-indol-3-yl)-1-({methyl[(1S)-2-(methylamino)-1-(2-naphthylmethyl)ethyl]amino}methyl)ethyl]-1,1'-biphenyl-4-carboxamide	4.9	5	2	2
20	 [Boc-L-(2-Naphthyl)-alanine][Boc-L-Tryptophan(Formyl)][4-Biphenylacetic acid]	608.8	608.4	2-(1,1'-biphenyl-4-yl)-N-[(1S)-2-(1-methyl-1H-indol-3-yl)-1-({methyl[(1S)-2-(methylamino)-1-(2-naphthylmethyl)ethyl]amino}methyl)ethyl]acetamide	4.8	5	2	2
21	 [Boc-L-(2-Naphthyl)-alanine][Boc-L-(2-Naphthyl)-alanine][4-Vinylbenzoic acid]	541.7	541.3	N-[(1S)-2-{methyl[(1S)-2-(methylamino)-1-(2-naphthylmethyl)ethyl]amino}-1-(2-naphthylmethyl)ethyl]-4-vinylbenzamide	5.6	4	2	2
22	 [Boc-L-(2-Naphthyl)-alanine][Boc-L-(2-Naphthyl)-alanine][4-Ethyl-4-Biphenylcarboxylic acid]	619.9	619.4	4'-ethyl-N-[(1S)-2-{methyl[(1S)-2-(methylamino)-1-(2-naphthylmethyl)ethyl]amino}-1-(2-naphthylmethyl)ethyl]-1,1'-biphenyl-4-carboxamide	6.5	4	2	2
23	 [Boc-L-(2-Naphthyl)-alanine][Boc-L-(2-Naphthyl)-alanine][3,5-Bis-(trifluoromethyl)-phenylacetic acid]	665.7	665.3	2-[3,5-bis(trifluoromethyl)phenyl]-N-[(1S)-2-{methyl[(1S)-2-(methylamino)-1-(2-naphthylmethyl)ethyl]amino}-1-(2-naphthylmethyl)ethyl]acetamide	6.9	4	2	2
24	 [Boc-L-(2-Naphthyl)-alanine][Boc-L-(2-Naphthyl)-alanine][4-Biphenylcarboxylic acid]	591.8	591.3	N-[(1S)-2-{methyl[(1S)-2-(methylamino)-1-(2-naphthylmethyl)ethyl]amino}-1-(2-naphthylmethyl)ethyl]-1,1'-biphenyl-4-carboxamide	6.2	4	2	2

FIGURE 21A (cont.)

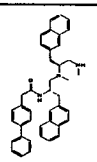
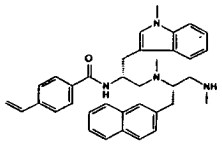
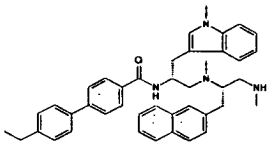
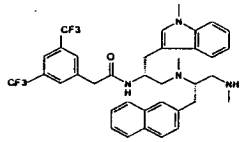
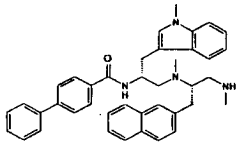
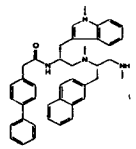
TPI1349	Structures FIGURE 21	MW	Exact Mass	Name	MLogP	HBondAcceptor	HBondDonor	RuleOfFive
25	 [Boc-L-(2-Naphthyl)-alanine][Boc-L-(2-Naphthyl)-alanine][4-Biphenylacetic acid]	605.8	605.3	2-(1,1'-biphenyl-4-yl)-N-[(1S)-2-{methyl[(1S)-2-(methylamino)-1-(2-naphthylmethyl)ethyl]amino}-1-(2-naphthylmethyl)ethyl]acetamide	6.1	4	2	2
26	 [Boc-L-(2-Naphthyl)-alanine][Boc-D-Tryptophan][4-Vinylbenzoic acid]	544.7	544.3	N-[(1R)-2-(1-methyl-1H-indol-3-yl)-1-({methyl[(1S)-2-(methylamino)-1-(2-naphthylmethyl)ethyl]amino}methyl)ethyl]-4-vinylbenzamide	4.3	5	2	2
27	 [Boc-L-(2-Naphthyl)-alanine][Boc-D-Tryptophan][4-Ethyl-4-Biphenylcarboxylic acid]	622.9	622.4	4'-ethyl-N-[(1R)-2-(1-methyl-1H-indol-3-yl)-1-({methyl[(1S)-2-(methylamino)-1-(2-naphthylmethyl)ethyl]amino}methyl)ethyl]-1,1'-biphenyl-4-carboxamide	5.2	5	2	2
28	 [Boc-L-(2-Naphthyl)-alanine][Boc-D-Tryptophan][3,5-Bis-(trifluoromethyl)-phenylacetic acid]	668.7	668.3	2-[3,5-bis(trifluoromethyl)phenyl]-N-[(1R)-2-(1-methyl-1H-indol-3-yl)-1-({methyl[(1S)-2-(methylamino)-1-(2-naphthylmethyl)ethyl]amino}methyl)ethyl]acetamide	5.6	5	2	2
29	 [Boc-L-(2-Naphthyl)-alanine][Boc-D-Tryptophan][4-Biphenylcarboxylic acid]	594.8	594.3	N-[(1R)-2-(1-methyl-1H-indol-3-yl)-1-({methyl[(1S)-2-(methylamino)-1-(2-naphthylmethyl)ethyl]amino}methyl)ethyl]-1,1'-biphenyl-4-carboxamide	4.9	5	2	2
30	 [Boc-L-(2-Naphthyl)-alanine][Boc-D-Tryptophan][4-Biphenylacetic acid]	608.8	608.4	2-(1,1'-biphenyl-4-yl)-N-[(1R)-2-(1-methyl-1H-indol-3-yl)-1-({methyl[(1S)-2-(methylamino)-1-(2-naphthylmethyl)ethyl]amino}methyl)ethyl]acetamide	4.8	5	2	2
TPI1349	Structures							

FIGURE 21A (cont.)

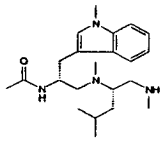
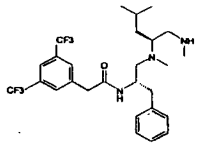
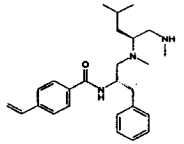
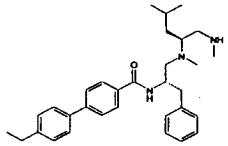
TPI1349	Structures FIGURE 21	MW	Exact Mass	Name	MLogP	HBondAcceptor	HBondDonor	RuleOfFive
31	 [Boc-L-Leucine][Boc-D-Tryptophan][Acetic acid]	372.6	372.3	N-{(1R)-2-(1-methyl-1H-indol-3-yl)-1-[(methyl{(1S)-3-methyl-1-[(methylamino)methyl]butyl}amino)methyl]ethyl}acetamide	2.0	5	2	0
TPI1349	Structures							
32	 [Boc-L-Leucine][Boc-L-Phenylalanine][3,5-Bis-(trifluoromethyl)-phenylacetic acid]	531.6	531.3	N-[(1S)-1-benzyl-2-(methyl{(1S)-3-methyl-1-[(methylamino)methyl]butyl}amino)ethyl]-2-[3,5-bis(trifluoromethyl)phenyl]acetamide	5.5	4	2	2
33	 [Boc-L-Leucine][Boc-L-Phenylalanine][4-Vinylbenzoic acid]	407.6	407.3	N-[(1S)-1-benzyl-2-(methyl{(1S)-3-methyl-1-[(methylamino)methyl]butyl}amino)ethyl]-4-vinylbenzamide	4.1	4	2	0
34	 [Boc-L-Leucine][Boc-L-Phenylalanine][4-Ethyl-4-Biphenylcarboxylic acid]	485.7	485.3	N-[(1S)-1-benzyl-2-(methyl{(1S)-3-methyl-1-[(methylamino)methyl]butyl}amino)ethyl]-4'-ethyl-1,1'-biphenyl-4-carboxamide	5.1	4	2	1

FIGURE 21A (cont.)

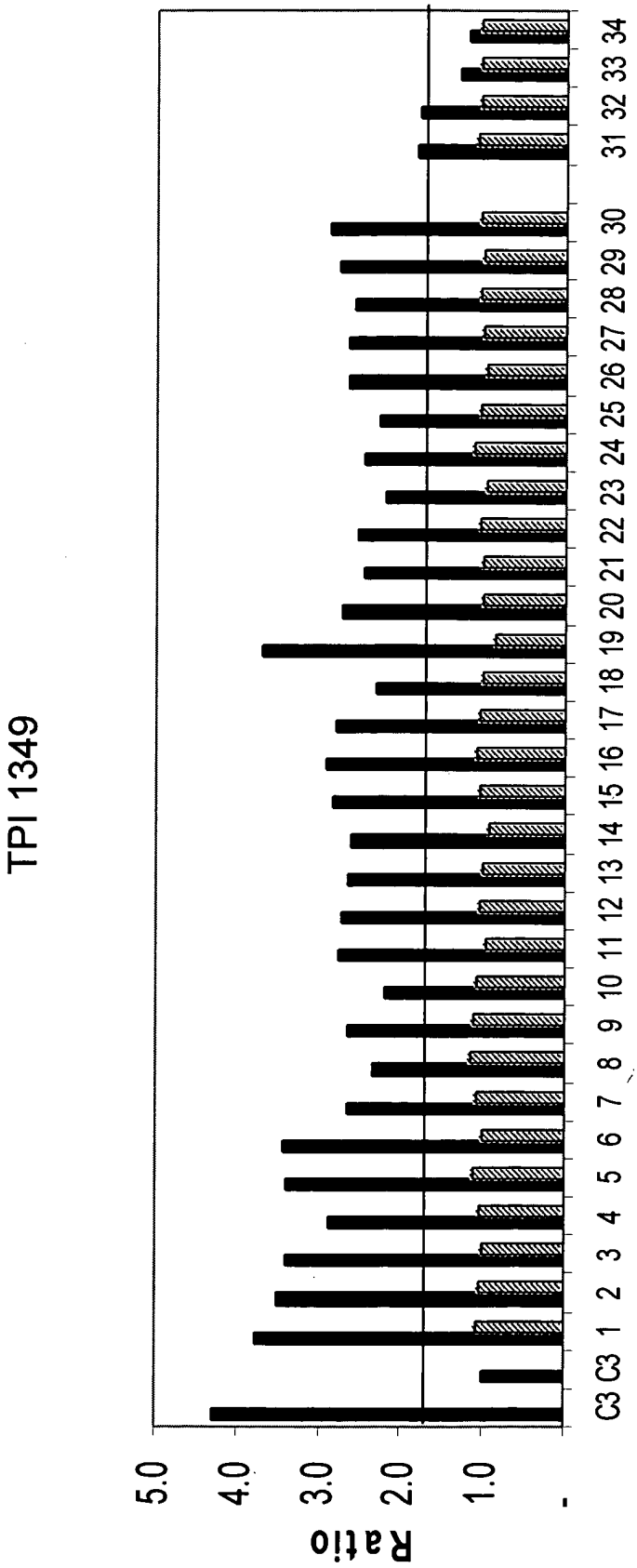

TPI 1349
Ratio
5.0
4.0
3.0
2.0
1.0
-
C3 C3 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34
+XIAP
TPI 1349-
25 µg/ml, (03/21/02)
XIAP
Caspase 3

Figure 21B

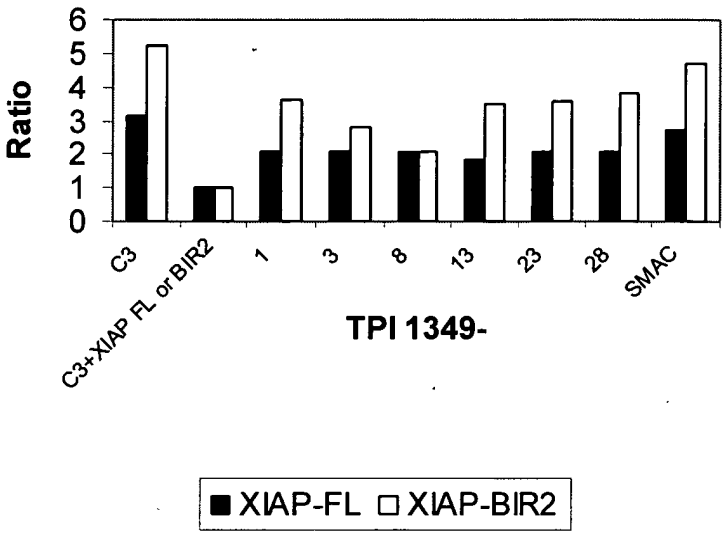
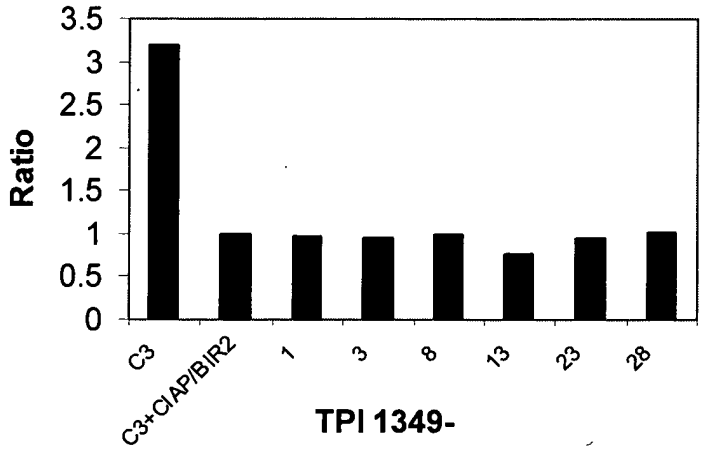

Ratio
6
5
4
3
2
1
0
C3
C3+XIAP FL or BIR2
1
3
8
13
23
28
SMAC
TPI 1349-
XIAP-FL
XIAP-BIR2

FIGURE 21C



100 μg/ml 10, 2003

FIGURE 21D

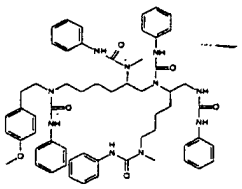
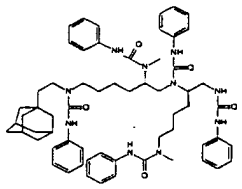
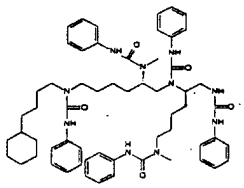
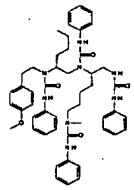
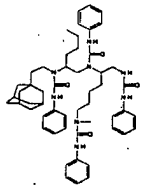
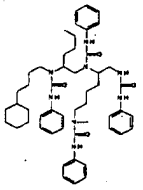
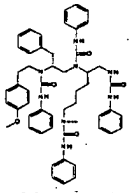
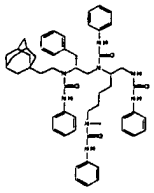
TPI1396	CHEMISTRY FIGURE 22	MW	Exact Mass	Name	MLogP	HBondAcceptor	HBondDonor	RuleOfFive
1	 [Boc-O-Lysine(2-Cl-Z)][a-CIZ-L-Lysine(e-Boc)][4-Methoxyphenylacetic acid]	1003.3	1002.5	N-[(5R)-6-[(anilinocarbonyl)amino]-5-[(anilinocarbonyl)[(2S)-6-[(anilinocarbonyl)[2-(4-methoxyphenyl)ethyl]amino]-2-[(anilinocarbonyl)(methyl)amino]hexyl]amino]hexyl]-N-methyl-N'-phenylurea	4.2	16	6	4
2	 [Boc-O-Lysine(2-Cl-Z)][a-CIZ-L-Lysine(e-Boc)][1-Adamantaneacetic acid]	1031.4	1030.6	N-[2-(1-adamantyl)ethyl]-N-[(5S)-6-[(anilinocarbonyl)[(1R)-1-[[(anilinocarbonyl)amino]methyl]-5-[(anilinocarbonyl)(methyl)amino]pentyl]amino]-5-[(anilinocarbonyl)(methyl)amino]hexyl]-N'-phenylurea	5.1	15	6	4
3	 [Boc-O-Lysine(2-Cl-Z)][a-CIZ-L-Lysine(e-Boc)][Cyclohexanebutyric acid]	1007.3	1006.6	N-[(5R)-6-[(anilinocarbonyl)amino]-5-[(anilinocarbonyl)[(2S)-6-[(anilinocarbonyl)(4-cyclohexylbutyl)amino]-2-[(anilinocarbonyl)(methyl)amino]hexyl]amino]hexyl]-N-methyl-N'-phenylurea	4.8	15	6	4
4	 [Boc-O-Lysine(2-Cl-Z)][Boc-L-Norleucine][4-Methoxyphenylacetic acid]	855.1	854.5	N-[(5R)-6-[(anilinocarbonyl)amino]-5-[(anilinocarbonyl)[(2S)-2-[(anilinocarbonyl)[2-(4-methoxyphenyl)ethyl]amino]hexyl]amino]hexyl]-N-methyl-N'-phenylurea	4.5	13	5	3
5	 [Boc-O-Lysine(2-Cl-Z)][Boc-L-Norleucine][1-Adamantaneacetic acid]	883.2	882.6	N-[2-(1-adamantyl)ethyl]-N-[(1S)-1-[[(anilinocarbonyl)[(1R)-1-[[(anilinocarbonyl)amino]methyl]-5-[(anilinocarbonyl)(methyl)amino]pentyl]amino]methyl]pentyl]-N'-phenylurea	5.5	12	5	3
6	 [Boc-O-Lysine(2-Cl-Z)][Boc-L-Norleucine][Cyclohexanebutyric acid]	859.2	858.6	N-[(5R)-6-[(anilinocarbonyl)amino]-5-[(anilinocarbonyl)[(2S)-2-[(anilinocarbonyl)(4-cyclohexylbutyl)amino]hexyl]amino]hexyl]-N-methyl-N'-phenylurea	5.2	12	5	3
7	 [Boc-O-Lysine(2-Cl-Z)][Boc-O-Phenylalanine][4-Methoxyphenylacetic acid]	889.1	888.5	N-[(5R)-6-[(anilinocarbonyl)amino]-5-[(anilinocarbonyl)[(2R)-2-[(anilinocarbonyl)[2-(4-methoxyphenyl)ethyl]amino]-3-phenylpropyl]amino]hexyl]-N-methyl-N'-phenylurea	4.8	13	5	3
8	 [Boc-O-Lysine(2-Cl-Z)][Boc-O-Phenylalanine][1-Adamantaneacetic acid]	917.2	916.5	N-[2-(1-adamantyl)ethyl]-N-[(1R)-2-[(anilinocarbonyl)[(1R)-1-[[(anilinocarbonyl)amino]methyl]-5-[(anilinocarbonyl)(methyl)amino]pentyl]amino]-1-benzylethyl]-N'-phenylurea	5.8	12	5	3

FIGURE 22A

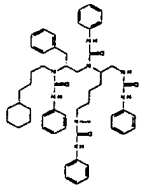
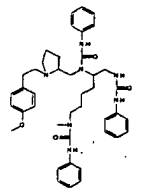
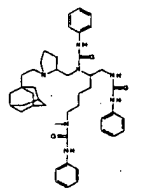
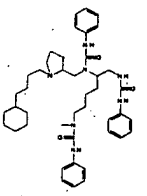
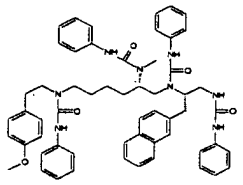
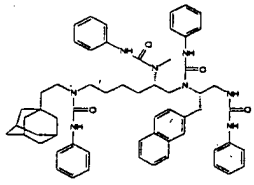
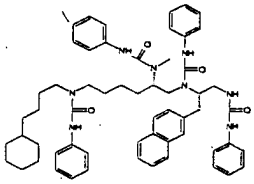
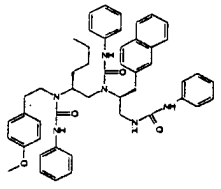
TPI1396	CHEMISTRY_FIGURE 22	MW	Exact Mass	Name	MLogP	HBondAcceptor	HBondDonor	RuleOfFive
9	 {Boc-D-Lysine(2-Cl-Z)}{Boc-D-Phenylalanine}[Cyclohexanebutyric acid]	893.2	892.5	N-{(5R)-6-{(anilinocarbonyl)amino}-5-{(anilinocarbonyl){(2R)-2-{(anilinocarbonyl){4-cyclohexylbutyl}amino}-3-phenylpropyl}amino}hexyl}-N-methyl-N'-phenylurea	5.5	12	5	3
10	 {Boc-D-Lysine(2-Cl-Z)}{Boc-L-Proline}[4-Methoxyphenylacetic acid]	719.9	719.4	N-{(5R)-6-{(anilinocarbonyl)amino}-5-{(anilinocarbonyl){{(2S)-1-[2-(4-methoxyphenyl)ethyl]pyrrolidin-2-yl}methyl}amino}hexyl}-N-methyl-N'-phenylurea	3.7	11	4	2
11	 {Boc-D-Lysine(2-Cl-Z)}{Boc-L-Proline}[1-Adamantaneacetic acid]	748.0	747.5	N-{{(2S)-1-[2-(1-adamantyl)ethyl]pyrrolidin-2-yl}methyl}-N-{(1R)-1-{[(anilinocarbonyl)amino]methyl}-5-{(anilinocarbonyl){methyl}amino}pentyl}-N'-phenylurea	4.9	10	4	2
12	 {Boc-D-Lysine(2-Cl-Z)}{Boc-L-Proline}[Cyclohexanebutyric acid]	724.0	723.5	N-{(5R)-6-{(anilinocarbonyl)amino}-5-{(anilinocarbonyl){[(2S)-1-(4-cyclohexylbutyl)pyrrolidin-2-yl]methyl}amino}hexyl}-N-methyl-N'-phenylurea	4.8	10	4	2
13	 {Boc-L-3-(2-Naphthyl)-Alanine}{a-ClZ-L-Lysine(e-Boc)}[4-Methoxyphenylacetic acid]	939.2	938.5	N-{(1S)-2-{(anilinocarbonyl)amino}-1-(2-naphthylmethyl)ethyl}-N-{(2S)-6-{(anilinocarbonyl){2-(4-methoxyphenyl)ethyl}amino}-2-{(anilinocarbonyl){methyl}amino}hexyl}-N'-phenylurea	5.2	13	5	3
14	 {Boc-L-3-(2-Naphthyl)-Alanine}{a-ClZ-L-Lysine(e-Boc)}[1-Adamantaneacetic acid]	967.3	966.6	N-[2-(1-adamantyl)ethyl]-N-{(5S)-6-{(anilinocarbonyl){(1S)-2-{(anilinocarbonyl)amino}-1-(2-naphthylmethyl)ethyl}amino}-5-{(anilinocarbonyl){methyl}amino}hexyl}-N'-phenylurea	6.2	12	5	3
15	 {Boc-L-3-(2-Naphthyl)-Alanine}{a-ClZ-L-Lysine(e-Boc)}[Cyclohexanebutyric acid]	943.2	942.6	N-{(1S)-2-{(anilinocarbonyl)amino}-1-(2-naphthylmethyl)ethyl}-N-{(2S)-6-{(anilinocarbonyl){4-cyclohexylbutyl}amino}-2-{(anilinocarbonyl){methyl}amino}hexyl}-N'-phenylurea	5.9	12	5	3
16	 {Boc-L-3-(2-Naphthyl)-Alanine}{Boc-L-Norleucine}[4-Methoxyphenylacetic acid]	791.0	790.4	N-{(1S)-2-{(anilinocarbonyl)amino}-1-(2-naphthylmethyl)ethyl}-N-{(2S)-2-{(anilinocarbonyl){2-(4-methoxyphenyl)ethyl}amino}hexyl}-N'-phenylurea	5.6	10	4	2

FIGURE 22A (cont.)

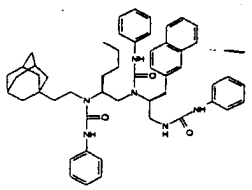
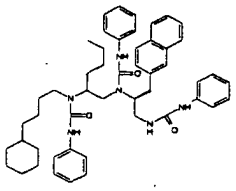
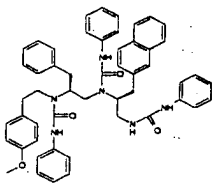
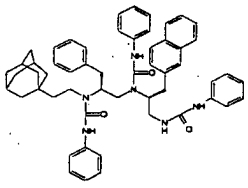
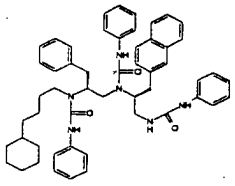
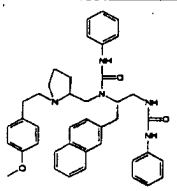
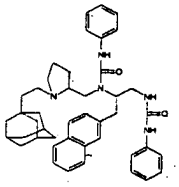
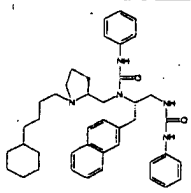
TPI1398	CHEMISTRY FIGURE 22	MW	Exact Mass	Name	MLogP	HBondAcceptor	HBondDonor	RuleOfFive
17	 [Boc-L-3-(2-Naphthyl)-Alanine][Boc-L-Norleucine][1-Adamantaneacetic acid]	819.1	818.5	N-[2-(1-adamantyl)ethyl]-N-[(1S)-1-({anilinocarbonyl}[(1S)-2-[anilinocarbonyl)amino]-1-(2-naphthylmethyl)ethyl]amino}methyl)pentyl]-N'-phenylurea	6.3	9	4	2
18	 [Boc-L-3-(2-Naphthyl)-Alanine][Boc-L-Norleucine][Cyclohexanebutyric acid]	795.1	794.5	N-[(1S)-2-[(anilinocarbonyl)amino]-1-(2-naphthylmethyl)ethyl]-N-[(2S)-2-[(anilinocarbonyl)(4-cyclohexylbutyl)amino]hexyl]-N'-phenylurea	6.0	9	4	2
19	 [Boc-L-3-(2-Naphthyl)-Alanine][Boc-O-Phenylalanine][4-Methoxyphenylacetic acid]	825.0	824.4	N-[(1S)-2-[(anilinocarbonyl)amino]-1-(2-naphthylmethyl)ethyl]-N-[(2S)-2-[(anilinocarbonyl)[2-(4-methoxyphenyl)ethyl]amino]-3-phenylpropyl]-N'-phenylurea	5.9	10	4	2
20	 [Boc-L-3-(2-Naphthyl)-Alanine][Boc-O-Phenylalanine][1-Adamantaneacetic acid]	853.1	852.5	N-[2-(1-adamantyl)ethyl]-N-[(1S)-2-({anilinocarbonyl}[(1S)-2-[(anilinocarbonyl)amino]-1-(2-naphthylmethyl)ethyl]amino}-1-benzylethyl)-N'-phenylurea	6.6	9	4	2
21	 [Boc-L-3-(2-Naphthyl)-Alanine][Boc-O-Phenylalanine][Cyclohexanebutyric acid]	829.1	828.5	N-[(1S)-2-[(anilinocarbonyl)amino]-1-(2-naphthylmethyl)ethyl]-N-[(2S)-2-[(anilinocarbonyl)(4-cyclohexylbutyl)amino]-3-phenylpropyl]-N'-phenylurea	6.3	9	4	2
22	 [Boc-L-3-(2-Naphthyl)-Alanine][Boc-L-Proline][4-Methoxyphenylacetic acid]	655.8	655.4	N-[(1S)-2-[(anilinocarbonyl)amino]-1-(2-naphthylmethyl)ethyl]-N-[(2S)-1-[2-(4-methoxyphenyl)ethyl]pyrrolidin-2-yl]methyl)-N'-phenylurea	4.6	8	3	2
23	 [Boc-L-3-(2-Naphthyl)-Alanine][Boc-L-Proline][1-Adamantaneacetic acid]	683.9	683.4	N-({(2S)-1-[2-(1-adamantyl)ethyl]pyrrolidin-2-yl}methyl)-N-[(1S)-2-[(anilinocarbonyl)amino]-1-(2-naphthylmethyl)ethyl]-N'-phenylurea	5.8	7	3	2
24	 [Boc-L-3-(2-Naphthyl)-Alanine][Boc-L-Proline][Cyclohexanebutyric acid]	659.9	659.4	N-[(1S)-2-[(anilinocarbonyl)amino]-1-(2-naphthylmethyl)ethyl]-N-[[(2S)-1-(4-cyclohexylbutyl)pyrrolidin-2-yl]methyl]-N'-phenylurea	5.4	7	3	2

FIGURE 22A (cont.)

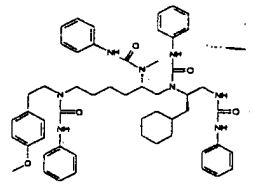
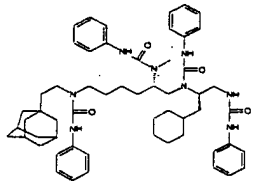
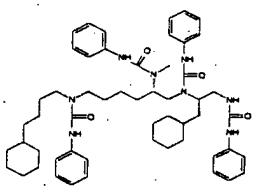
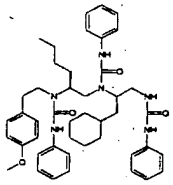
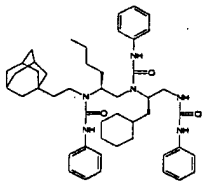
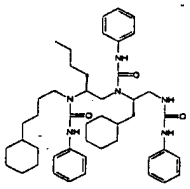
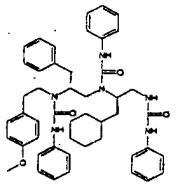
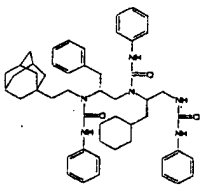
TPI1396	CHEMISTRY_FIGURE 22	MW	Exact Mass	Name	MLogP	HBondAcceptor	HBondDonor	RuleOfFive
25	 [Boc-D-Cyclohexylalanine][a-CIZ-L-Lysine(e-Boc)][4-Methoxyphenylacetic acid]	895.2	894.5	N-{(1R)-2-[(anilinocarbonyl)amino]-1-(cyclohexylmethyl)ethyl}-N~6~-{(2S)-6-[(anilinocarbonyl)(2-(4-methoxyphenyl)ethyl]amino}-2-[(anilinocarbonyl)(methyl)amino]hexyl}-N'-phenylurea	4.6	13	5	3
26	 [Boc-D-Cyclohexylalanine][a-CIZ-L-Lysine(e-Boc)][1-Adamantaneacetic acid]	923.3	922.6	N-{2-(1-adamantyl)ethyl}-N~6~-{(5S)-6-[(anilinocarbonyl)(1R)-2-[(anilinocarbonyl)amino]-1-(cyclohexylmethyl)ethyl]amino}-5-[(anilinocarbonyl)(methyl)amino]hexyl}-N'-phenylurea	8.0	12	5	3
27	 [Boc-D-Cyclohexylalanine][a-CIZ-L-Lysine(e-Boc)][Cyclohexanebutyric acid]	899.2	898.6	N-{(1R)-2-[(anilinocarbonyl)amino]-1-(cyclohexylmethyl)ethyl}-N~6~-{(2S)-6-[(anilinocarbonyl)(4-cyclohexylbutyl)amino]-2-[(anilinocarbonyl)(methyl)amino]hexyl}-N'-phenylurea	5.7	12	5	3
28	 [Boc-D-Cyclohexylalanine][Boc-L-Norleucine][4-Methoxyphenylacetic acid]	747.0	746.5	N-{(1R)-2-[(anilinocarbonyl)amino]-1-(cyclohexylmethyl)ethyl}-N~6~-{(2S)-2-[(anilinocarbonyl)(2-(4-methoxyphenyl)ethyl]amino}hexyl}-N'-phenylurea	4.9	10	4	2
29	 [Boc-D-Cyclohexylalanine][Boc-L-Norleucine][1-Adamantaneacetic acid]	775.1	774.5	N-{2-(1-adamantyl)ethyl}-N~6~-{(1S)-1-({(anilinocarbonyl)[(1R)-2-[(anilinocarbonyl)amino]-1-(cyclohexylmethyl)ethyl]amino}methyl)pentyl}-N'-phenylurea	6.1	9	4	2
30	 [Boc-D-Cyclohexylalanine][Boc-L-Norleucine][Cyclohexanebutyric acid]	751.1	750.5	N-{(1R)-2-[(anilinocarbonyl)amino]-1-(cyclohexylmethyl)ethyl}-N~6~-{(2S)-2-[(anilinocarbonyl)(4-cyclohexylbutyl)amino]hexyl}-N'-phenylurea	5.8	9	4	2
31	 [Boc-D-Cyclohexylalanine][Boc-D-Phenylalanine][4-Methoxyphenylacetic acid]	781.0	780.4	N-{(1R)-2-[(anilinocarbonyl)amino]-1-(cyclohexylmethyl)ethyl}-N~6~-{(2R)-2-[(anilinocarbonyl)(2-(4-methoxyphenyl)ethyl]amino}-3-phenylpropyl}-N'-phenylurea	5.2	10	4	2
32	 [Boc-D-Cyclohexylalanine][Boc-D-Phenylalanine][1-Adamantaneacetic acid]	809.1	808.5	N-{2-(1-adamantyl)ethyl}-N~6~-{(1R)-2-[(anilinocarbonyl)(1R)-2-[(anilinocarbonyl)amino]-1-(cyclohexylmethyl)ethyl]amino}-1-benzylethyl}-N'-phenylurea	6.4	9	4	2

FIGURE 22A (cont.)

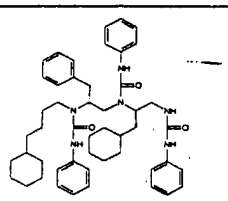
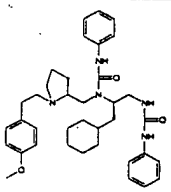
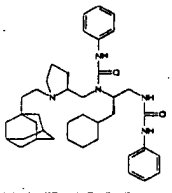
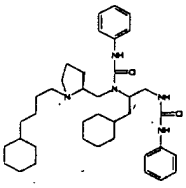
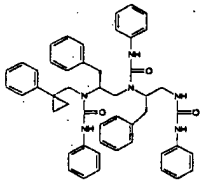
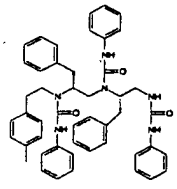
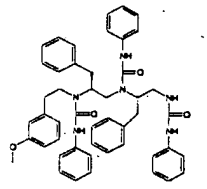
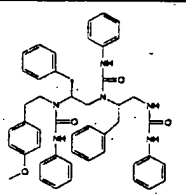
TPI1396	CHEMISTRY FIGURE 22	MW	Exact Mass	Name	MLogP	HBondAcceptor	HBondDonor	RuleOfFive
33	 [Boc-D-Cyclohexylalanine][Boc-D-Phenylalanine][Cyclohexanebutyric acid]	785.1	784.5	N-{(1R)-2-[(anilinocarbonyl)amino]-1-(cyclohexylmethyl)ethyl}-N-{(2R)-2-[(anilinocarbonyl)(4-cyclohexylbutyl)amino]-3-phenylpropyl}-N'-phenylurea	6.0	9	4	2
34	 [Boc-D-Cyclohexylalanine][Boc-L-Proline][4-Methoxyphenylacetic acid]	611.8	611.4	N-{(1R)-2-[(anilinocarbonyl)amino]-1-(cyclohexylmethyl)ethyl}-N-{[(2S)-1-[2-(4-methoxyphenyl)ethyl]pyrrolidin-2-yl]methyl}-N'-phenylurea	4.3	8	3	2
35	 [Boc-D-Cyclohexylalanine][Boc-L-Proline][1-Adamantaneacetic acid]	639.9	639.5	N-{[(2S)-1-[2-(1-adamantyl)ethyl]pyrrolidin-2-yl]methyl}-N-{(1R)-2-[(anilinocarbonyl)amino]-1-(cyclohexylmethyl)ethyl}-N'-phenylurea	5.5	7	3	2
36	 [Boc-D-Cyclohexylalanine][Boc-L-Proline][Cyclohexanebutyric acid]	615.9	615.5	N-{(1R)-2-[(anilinocarbonyl)amino]-1-(cyclohexylmethyl)ethyl}-N-{[(2S)-1-(4-cyclohexylbutyl)pyrrolidin-2-yl]methyl}-N'-phenylurea	5.1	7	3	2
	CHEMISTRY							
37	 [Boc-L-Phenylalanine][Boc-L-Phenylalanine][1-Phenyl-1-Cyclopropanecarboxylic acid]	771.0	770.4	N-((1S)-2-[(anilinocarbonyl)amino]-1-benzylethyl)-N-{(2S)-2-[(anilinocarbonyl)(1-phenylcyclopropyl)methyl]amino}-3-phenylpropyl)-N'-phenylurea	5.7	9	4	2
38	 [Boc-L-Phenylalanine][Boc-L-Phenylalanine][p-Tolylacetic acid]	759.0	758.4	N-((1S)-2-[(anilinocarbonyl)amino]-1-benzylethyl)-N-((2S)-2-[(anilinocarbonyl)(2-(4-methylphenyl)ethyl]amino}-3-phenylpropyl)-N'-phenylurea	5.9	9	4	2
39	 [Boc-L-Phenylalanine][Boc-L-Phenylalanine][3-Methoxyphenylacetic acid]	775.0	774.4	N-((1S)-2-[(anilinocarbonyl)amino]-1-benzylethyl)-N-((2S)-2-[(anilinocarbonyl)(2-(3-methoxyphenyl)ethyl]amino}-3-phenylpropyl)-N'-phenylurea	5.4	10	4	2
40	 [Boc-L-Phenylalanine][Boc-L-Phenylalanine][4-Methoxyphenylacetic acid]	775.0	774.4	N-((1S)-2-[(anilinocarbonyl)amino]-1-benzylethyl)-N-((2S)-2-[(anilinocarbonyl)(2-(4-methoxyphenyl)ethyl]amino}-3-phenylpropyl)-N'-phenylurea	5.4	10	4	2

FIGURE 22A (cont.)

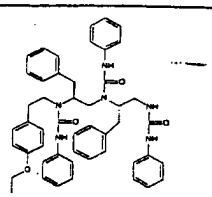
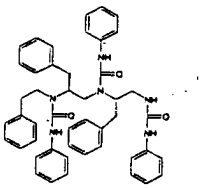
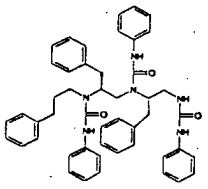
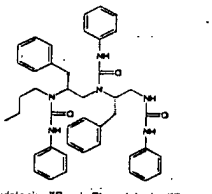
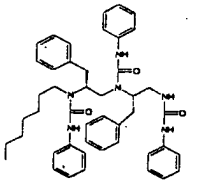
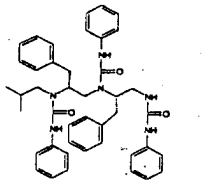
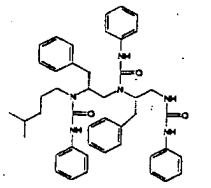
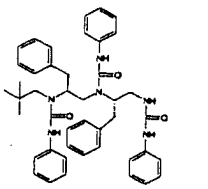
TPI1396	CHEMISTRY FIGURE 22	MW	Exact Mass	Name	MLogP	HBondAcceptor	HBondDonor	RuleOfFive
41	 [Boc-L-Phenylalanine][Boc-L-Phenylalanine][4-Ethoxyphenylacetic acid]	789.0	788.4	N-{(1S)-2-[(anilinocarbonyl)amino]-1-benzylethyl}-N-{(2S)-2-[(anilinocarbonyl)(2-(4-ethoxyphenyl)ethyl]amino}-3-phenylpropyl}-N'-phenylurea	5.6	10	4	2
42	 [Boc-L-Phenylalanine][Boc-L-Phenylalanine][Phenylacetic acid]	744.9	744.4	N-{(1S)-2-[(anilinocarbonyl)amino]-1-benzylethyl}-N-{(2S)-2-[(anilinocarbonyl)(2-phenylethyl)amino]-3-phenylpropyl}-N'-phenylurea	5.7	9	4	2
43	 [Boc-L-Phenylalanine][Boc-L-Phenylalanine][Hydrocinnamic acid]	759.0	758.4	N-{(1S)-2-[(anilinocarbonyl)amino]-1-benzylethyl}-N-{(2S)-2-[(anilinocarbonyl)(3-phenylpropyl)amino]-3-phenylpropyl}-N'-phenylurea	5.9	9	4	2
44	 [Boc-L-Phenylalanine][Boc-L-Phenylalanine][Butyric acid]	696.9	696.4	N-{(1S)-2-[(anilinocarbonyl)amino]-1-benzylethyl}-N-{(2S)-2-[(anilinocarbonyl)(butyl)amino]-3-phenylpropyl}-N'-phenylurea	5.3	9	4	2
45	 [Boc-L-Phenylalanine][Boc-L-Phenylalanine][Heptanoic acid]	739.0	738.4	N-{(1S)-2-[(anilinocarbonyl)amino]-1-benzylethyl}-N-{(2S)-2-[(anilinocarbonyl)(heptyl)amino]-3-phenylpropyl}-N'-phenylurea	5.8	9	4	2
46	 [Boc-L-Phenylalanine][Boc-L-Phenylalanine][Isobutyric acid]	696.9	696.4	N-{(1S)-2-[(anilinocarbonyl)amino]-1-benzylethyl}-N-{(2S)-2-[(anilinocarbonyl)(isobutyl)amino]-3-phenylpropyl}-N'-phenylurea	5.3	9	4	2
47	 [Boc-L-Phenylalanine][Boc-L-Phenylalanine][4-Methylvaleric acid]	724.9	724.4	N-{(1S)-2-[(anilinocarbonyl)amino]-1-benzylethyl}-N-{(2S)-2-[(anilinocarbonyl)(4-methylpentyl)amino]-3-phenylpropyl}-N'-phenylurea	5.8	9	4	2
48	 [Boc-L-Phenylalanine][Boc-L-Phenylalanine][Trimethylacetic acid]	710.9	710.4	N-{(1S)-2-[(anilinocarbonyl)amino]-1-benzylethyl}-N-{(2S)-2-[(anilinocarbonyl)(neopentyl)amino]-3-phenylpropyl}-N'-phenylurea	5.4	9	4	2

FIGURE 22A (cont.)

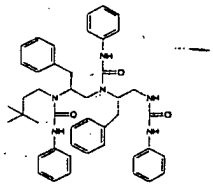
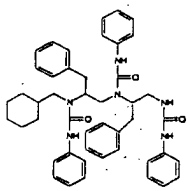
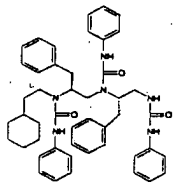
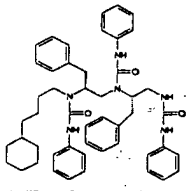
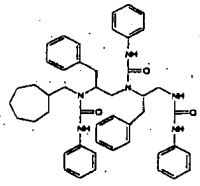
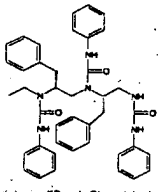
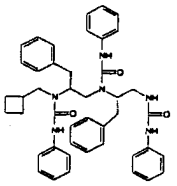
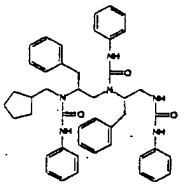
TPI1396	CHEMISTRY FIGURE 22	MW	Exact Mass	Name	MLogP	HBondAcceptor	HBondDonor	RuleOfFive
49	 [Boc-L-Phenylalanine][Boc-L-Phenylalanine][tert-Butylacetic acid]	724.9	724.4	N-[(1S)-2-[(anilinocarbonyl)amino]-1-benzylethyl]-N-[(2S)-2-[(anilinocarbonyl)(3,3-dimethylbutyl)amino]-3-phenylpropyl]-N'-phenylurea	5.6	9	4	2
50	 [Boc-L-Phenylalanine][Boc-L-Phenylalanine][Cyclohexanecarboxylic acid]	737.0	736.4	N-[(1S)-2-[(anilinocarbonyl)amino]-1-benzylethyl]-N-[(2S)-2-[(anilinocarbonyl)(cyclohexylmethyl)amino]-3-phenylpropyl]-N'-phenylurea	5.4	9	4	2
51	 [Boc-L-Phenylalanine][Boc-L-Phenylalanine][Cyclohexylacetic acid]	751.0	750.4	N-[(1S)-2-[(anilinocarbonyl)amino]-1-benzylethyl]-N-[(2S)-2-[(anilinocarbonyl)(2-cyclohexylethyl)amino]-3-phenylpropyl]-N'-phenylurea	5.5	9	4	2
52	 [Boc-L-Phenylalanine][Boc-L-Phenylalanine][Cyclohexanebutyric acid]	779.0	778.5	N-[(1S)-2-[(anilinocarbonyl)amino]-1-benzylethyl]-N-[(2S)-2-[(anilinocarbonyl)(4-cyclohexylbutyl)amino]-3-phenylpropyl]-N'-phenylurea	5.8	9	4	2
53	 [Boc-L-Phenylalanine][Boc-L-Phenylalanine][Cycloheptanecarboxylic acid]	751.0	750.4	N-[(1S)-2-[(anilinocarbonyl)amino]-1-benzylethyl]-N-[(2S)-2-[(anilinocarbonyl)(cycloheptylmethyl)amino]-3-phenylpropyl]-N'-phenylurea	5.5	9	4	2
54	 [Boc-L-Phenylalanine][Boc-L-Phenylalanine][Acetic acid]	668.8	668.3	N-[(1S)-2-[(anilinocarbonyl)amino]-1-benzylethyl]-N-[(2S)-2-[(anilinocarbonyl)(ethyl)amino]-3-phenylpropyl]-N'-phenylurea	4.9	9	4	2
55	 [Boc-L-Phenylalanine][Boc-L-Phenylalanine][Cyclobutanecarboxylic acid]	708.9	708.4	N-[(1S)-2-[(anilinocarbonyl)amino]-1-benzylethyl]-N-[(2S)-2-[(anilinocarbonyl)(cyclobutylmethyl)amino]-3-phenylpropyl]-N'-phenylurea	5.0	9	4	2
56	 [Boc-L-Phenylalanine][Boc-L-Phenylalanine][Cyclopentanecarboxylic acid]	722.9	722.4	N-[(1S)-2-[(anilinocarbonyl)amino]-1-benzylethyl]-N-[(2S)-2-[(anilinocarbonyl)(cyclopentylmethyl)amino]-3-phenylpropyl]-N'-phenylurea	5.2	9	4	2

FIGURE 22A (cont.)

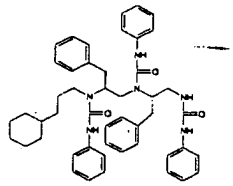
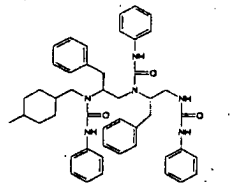
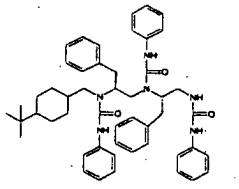
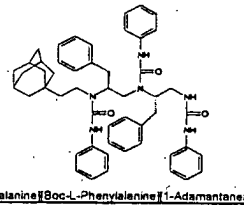
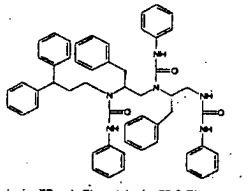
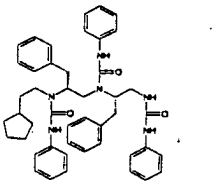
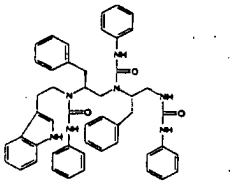
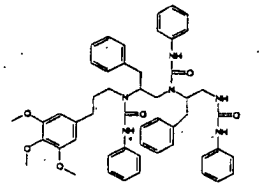
TPI1396	CHEMISTRY_FIGURE 22	MW	Exact Mass	Name	MLogP	HBondAcceptor	HBondDonor	RuleOfFive
57	 [Boc-L-Phenylalanine][Boc-L-Phenylalanine][Cyclohexanepropionic acid]	765.0	764.4	N-{(1S)-2-[(anilinocarbonyl)amino]-1-benzylethyl}-N-{(2S)-2-[(anilinocarbonyl)(3-cyclohexylpropyl)amino]-3-phenylpropyl}-N'-phenylurea	5.7	9	4	2
58	 [Boc-L-Phenylalanine][Boc-L-Phenylalanine][4-Methyl-1-cyclohexanecarboxylic acid]	751.0	750.4	N-{(1S)-2-[(anilinocarbonyl)amino]-1-benzylethyl}-N-{(2S)-2-[(anilinocarbonyl)(4-methylcyclohexyl)methyl]amino}-3-phenylpropyl}-N'-phenylurea	5.5	9	4	2
59	 [Boc-L-Phenylalanine][Boc-L-Phenylalanine][4-tert-Butyl-cyclohexanecarboxylic acid]	793.1	792.5	N-{(1S)-2-[(anilinocarbonyl)amino]-1-benzylethyl}-N-{(2S)-2-[(anilinocarbonyl)(4-tert-butylcyclohexyl)methyl]amino}-3-phenylpropyl}-N'-phenylurea	6.0	9	4	2
60	 [Boc-L-Phenylalanine][Boc-L-Phenylalanine][1-Adamantaneacetic acid]	803.1	802.5	N-[2-(1-adamantyl)ethyl]-N-{(1S)-2-[(anilinocarbonyl)((1S)-2-[(anilinocarbonyl)amino]-1-benzylethyl}amino)-1-benzylethyl}-N'-phenylurea	6.2	9	4	2
61	 [Boc-L-Phenylalanine][Boc-L-Phenylalanine][3,3-Diphenylpropionic acid]	835.1	834.4	N-{(1S)-2-[(anilinocarbonyl)amino]-1-benzylethyl}-N-{(2S)-2-[(anilinocarbonyl)(3,3-diphenylpropyl)amino]-3-phenylpropyl}-N'-phenylurea	6.6	9	4	2
62	 [Boc-L-Phenylalanine][Boc-L-Phenylalanine][Cyclopentylacetic acid]	737.0	736.4	N-{(1S)-2-[(anilinocarbonyl)amino]-1-benzylethyl}-N-{(2S)-2-[(anilinocarbonyl)(2-cyclopentylethyl)amino]-3-phenylpropyl}-N'-phenylurea	5.4	9	4	2
63	 [Boc-L-Phenylalanine][Boc-L-Phenylalanine][Indole-3-acetic acid]	784.0	783.4	N-{(1S)-2-[(anilinocarbonyl)amino]-1-benzylethyl}-N-{(2S)-2-[(anilinocarbonyl)(2-(1H-indol-3-yl)ethyl]amino}-3-phenylpropyl}-N'-phenylurea	4.8	10	5	2
64	 [Boc-L-Phenylalanine][Boc-L-Phenylalanine][3-(3,4,5)-Trimethoxyphenylpropionic acid]	849.0	848.4	N-{(1S)-2-[(anilinocarbonyl)amino]-1-benzylethyl}-N-{(2S)-2-[(anilinocarbonyl)(3-(3,4,5-trimethoxyphenyl)propyl]amino}-3-phenylpropyl}-N'-phenylurea	4.5	12	4	3

FIGURE 22A (cont.)

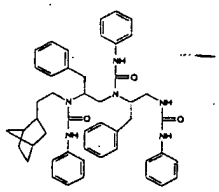
TPI1396	CHEMISTRY_FIGURE 22	MW	Exact Mass	Name	MLogP	HBondAcceptor	HBondDonor	RuleOfFive
85	 {Boc-L-Phenylalanine}{Boc-L-Phenylalanine}{2-Norbornaneacetic acid}	783.0	782.4	N-{(1S)-2-{(anilinocarbonyl)amino}-1-benzylethyl}-N-{(2S)-2-{(anilinocarbonyl)(2-bicyclo[2.2.1]hept-2-ylethyl)amino}-3-phenylpropyl}-N'-phenylurea	5.7	9	4	2

FIGURE 22A (cont.)

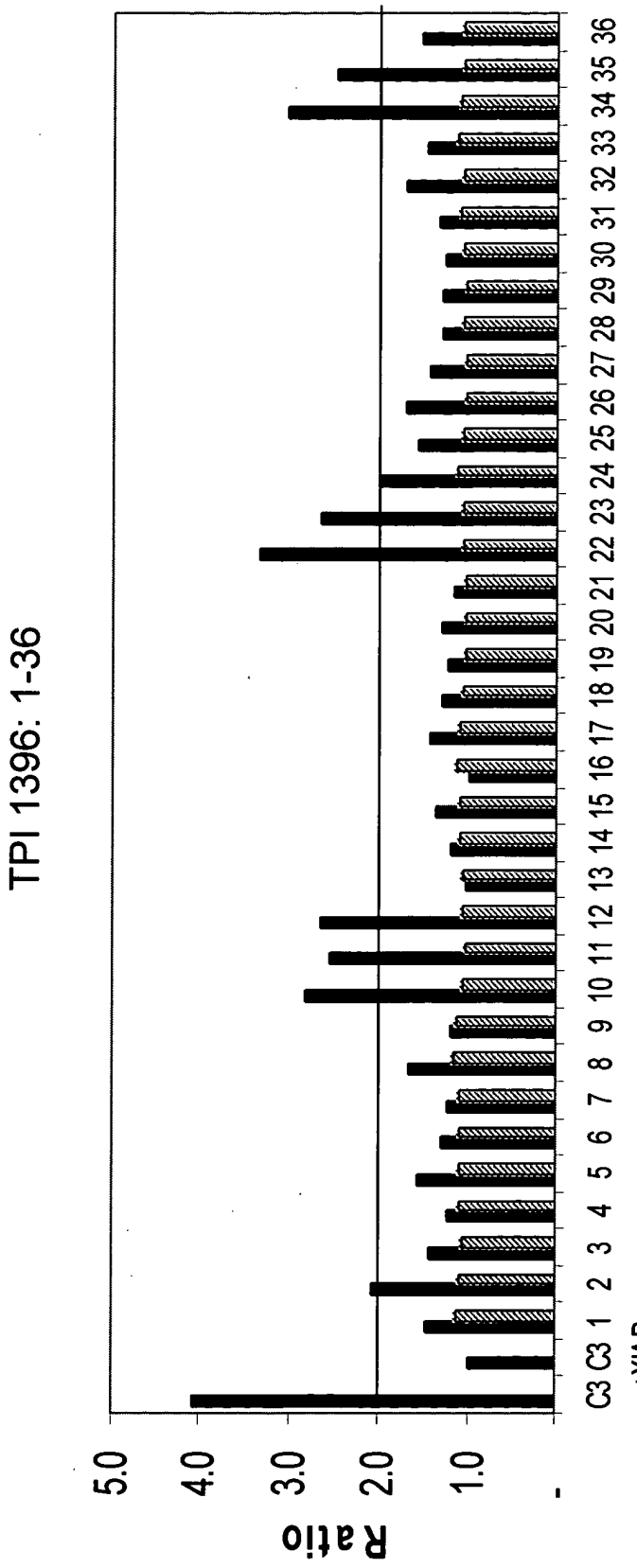

TPI 1396: 1-36
Ratio
5.0
4.0
3.0
2.0
1.0
-
C3 C3 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36
+XIAP
Compound #
XIAP Caspase 3
Screening @ 25 µg/ml

FIGURE 22B

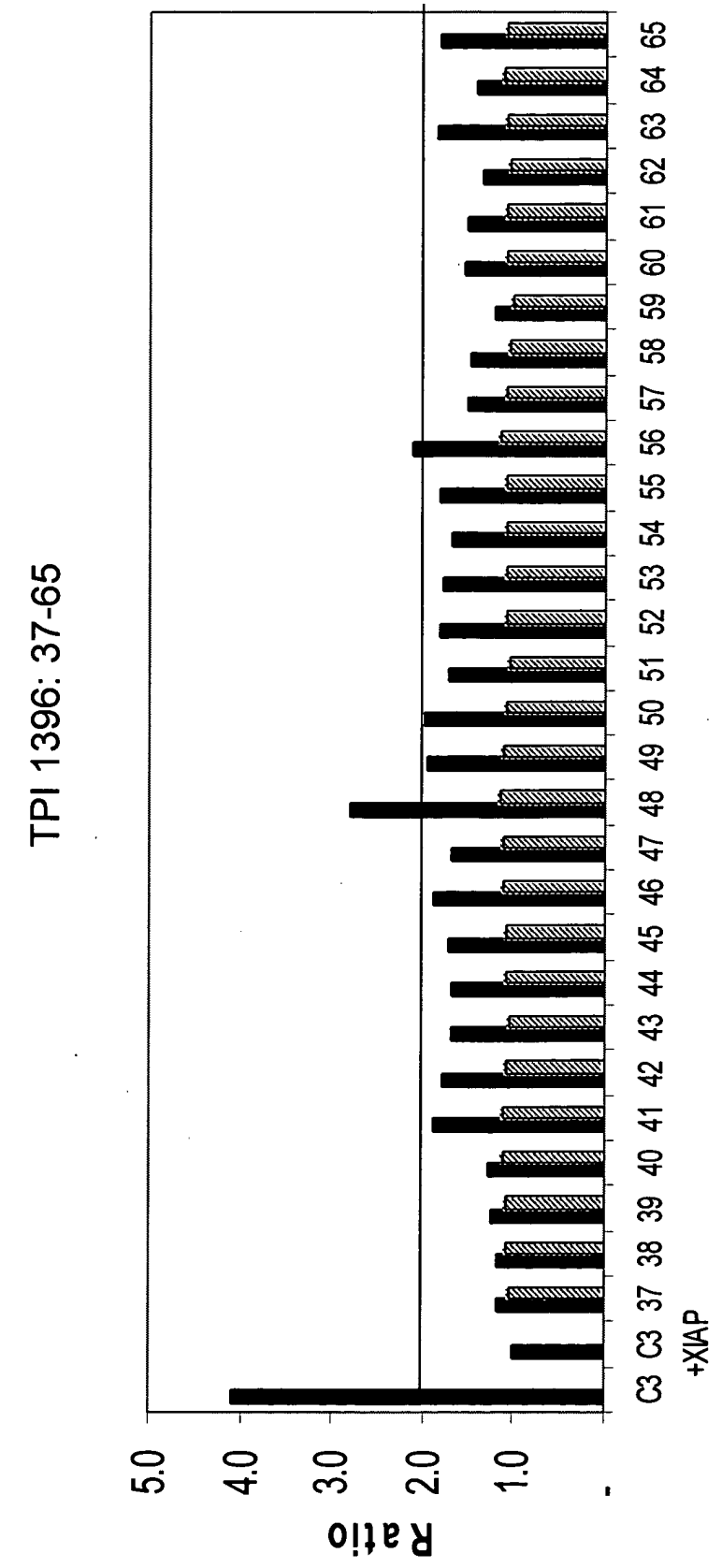
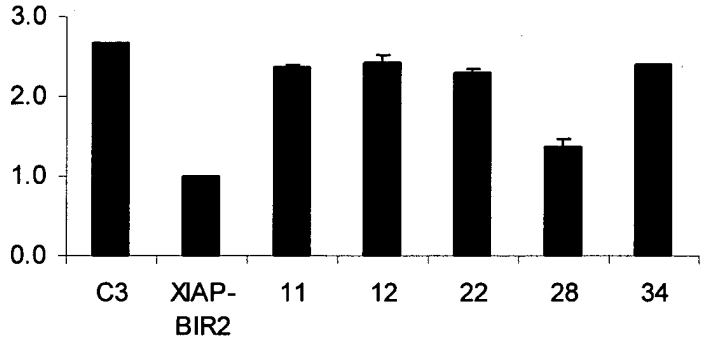

TPI 1396: 37-65
Ratio
5.0
4.0
3.0
2.0
1.0
-
C3 C3 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65
+XIAP
Compound #
XIAP Caspase 3
Screening @ 25 µg/ml

FIGURE 22C

Selected TPI 1396

TPI 1396	Caspase 3-XIAP IC-50 (μM)		Caspase 3-XIAP-BIR2 IC-50 (μM)	
	AVG	STD	**AVG**	STD
11	**32.1**	3.8	**7.9**	0.3
12	**53.0**	8.3	**14.4**	1.1
22	**45.3**	3.3	**9.5**	2.2
28	**>134**		**134.1**	0.3
34	**77.1**	11.0	**13.6**	0.9

FIGURE 22D



TPI 1396-

50 μg/ml-Data 02,2003

FIGURE 22E

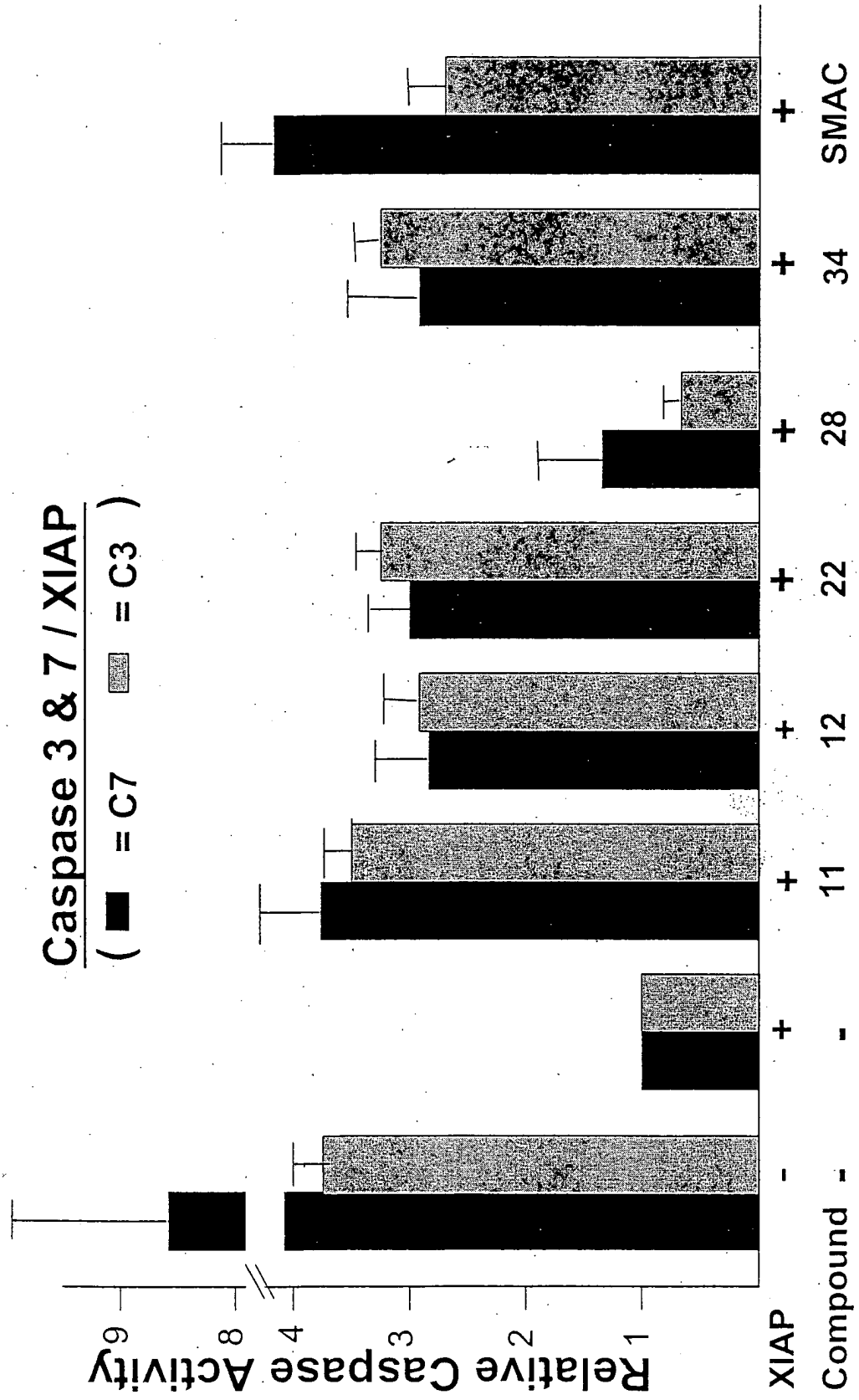

Caspase 3 & 7 / XIAP
(■ = C7 ▒ = C3)
Relative Caspase Activity
1
2
3
4
8
6
XIAP
Compound
-
+
-
+
+
+
+
+
+
11
12
22
28
34
SMAC

FIGURE 22F

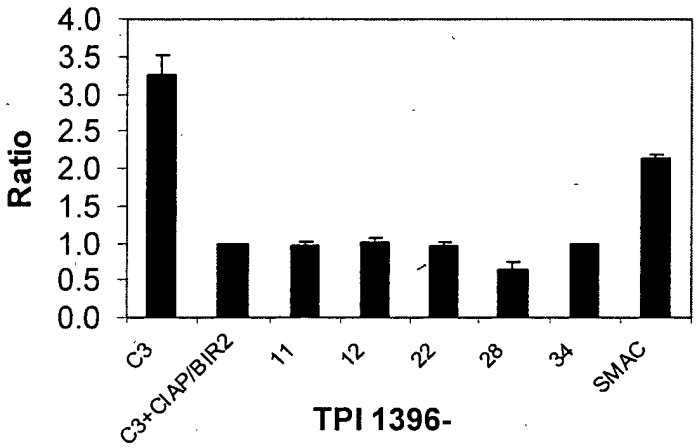

4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Ratio
C3
C3+ClAP/BIR2
11
12
22
28
34
SMAC
TPI 1396-

FIGURE 22G

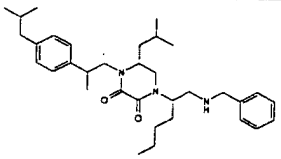
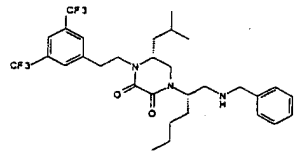
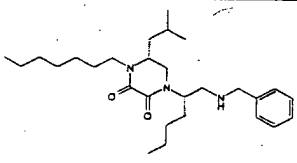
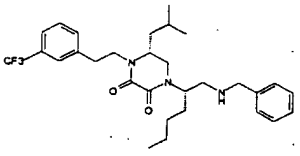
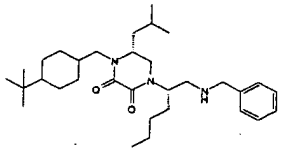
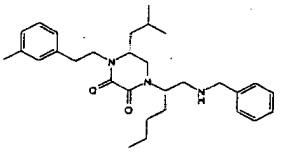
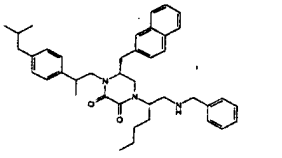
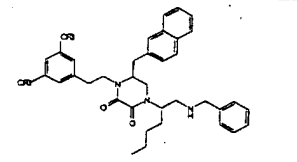
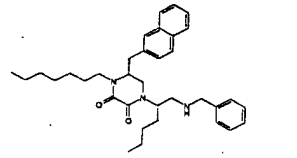
TPI1391	Structures FIGURE 23A	MW	Exact Mass	Name	MLogP	HBondDonor	HBondDonor	RuleOfFive
1	 [Fmoc-L-Norleucine][Fmoc-D-Leucine][4-Isobutyl-alpha-Methylphenylacetic Acid]	533.8	533.4	(5R)-1-{(1S)-1-[(benzylamino)methyl]pentyl}-5-isobutyl-4-[2-(4-isobutylphenyl)propyl]piperazine-2,3-dione	4.8	5	1	2
2	 Accord For Excel - New Chemistry	599.7	599.3	(5R)-1-{(1S)-1-[(benzylamino)methyl]pentyl}-4-[2-[3,5-bis(trifluoromethyl)phenyl]ethyl]-5-isobutylpiperazine-2,3-dione	5.4	5	1	2
3	 [Fmoc-L-Norleucine][Fmoc-D-Leucine][Heptanoic acid]	457.7	457.4	(5R)-1-{(1S)-1-[(benzylamino)methyl]pentyl}-4-heptyl-5-isobutylpiperazine-2,3-dione	3.7	5	1	0
4	 [Fmoc-L-Norleucine][Fmoc-D-Leucine][(Alpha,Alpha,Alpha-Trifluoro-m-Tolyl) acetic acid]	531.7	531.3	(5R)-1-{(1S)-1-[(benzylamino)methyl]pentyl}-5-isobutyl-4-[2-[3-(trifluoromethyl)phenyl]ethyl]piperazine-2,3-dione	4.4	5	1	2
5	 [Fmoc-L-Norleucine][Fmoc-D-Leucine][4-tert-Butyl-cyclohexanecarboxylic acid]	511.8	511.4	(5R)-1-{(1S)-1-[(benzylamino)methyl]pentyl}-4-{(4-tert-butylcyclohexyl)methyl}-5-isobutylpiperazine-2,3-dione	4.5	5	1	2
6	 [Fmoc-L-Norleucine][Fmoc-D-Leucine][m-Tolylacetic acid]	477.7	477.3	(5R)-1-{(1S)-1-[(benzylamino)methyl]pentyl}-5-isobutyl-4-[2-(3-methylphenyl)ethyl]piperazine-2,3-dione	3.9	5	1	0
7	 [Fmoc-L-Norleucine][Fmoc-L-2-Naphthylalanine][4-Isobutyl-alpha-Methylphenylacetic Acid]	617.9	617.4	(5S)-1-{(1S)-1-[(benzylamino)methyl]pentyl}-4-[2-(4-isobutylphenyl)propyl]-5-(2-naphthylmethyl)piperazine-2,3-dione	5.4	5	1	2
8	 [Fmoc-L-Norleucine][Fmoc-L-2-Naphthylalanine][3,5-Bis(Trifluoromethyl)-Phenylacetic Acid]	683.7	683.3	(5S)-1-{(1S)-1-[(benzylamino)methyl]pentyl}-4-[2-[3,5-bis(trifluoromethyl)phenyl]ethyl]-5-(2-naphthylmethyl)piperazine-2,3-dione	6.2	5	1	2
9	 [Fmoc-L-Norleucine][Fmoc-L-2-Naphthylalanine][Heptanoic acid]	541.8	541.4	(5S)-1-{(1S)-1-[(benzylamino)methyl]pentyl}-4-heptyl-5-(2-naphthylmethyl)piperazine-2,3-dione	4.8	5	1	2

FIGURE 23A

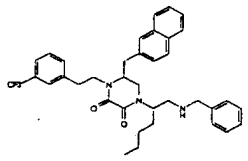
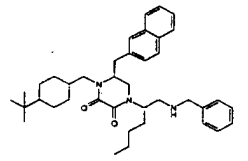
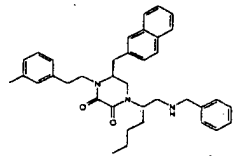
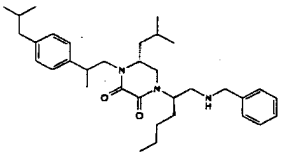
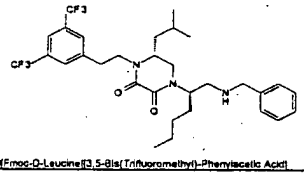
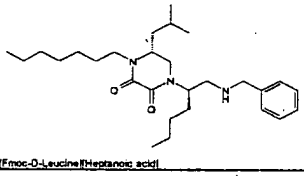
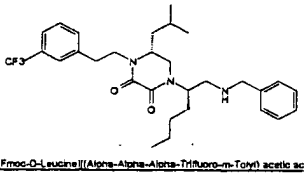
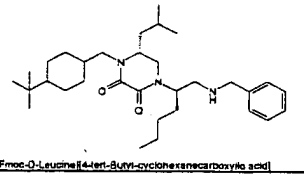
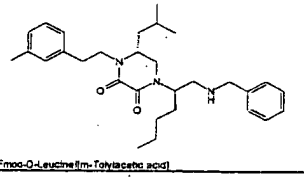
TPI1391	Structures FIGURE 23A	MW	Exact Mass	Name	MLogP	HBondDonor	HBondDonor	RuleOfFive
10	 [Fmoc-L-Norleucine][Fmoc-L-2-Naphthylalanine][(Alpha,-Alpha-Alpha-Trifluoro-m-Tolyl) acetic acid]	615.7	615.3	(5S)-1-((1S)-1-[(benzylamino)methyl]pentyl)-5-(2-naphthylmethyl)-4-(2-[3-(trifluoromethyl)phenyl]ethyl)piperazine-2,3-dione	5.3	5	1	2
11	 [Fmoc-L-Norleucine][Fmoc-L-2-Naphthylalanine][4-tert-Butyl-cyclohexanecarboxylic acid]	595.9	595.4	(5S)-1-((1S)-1-[(benzylamino)methyl]pentyl)-4-[(4-tert-butylcyclohexyl)methyl]-5-(2-naphthylmethyl)piperazine-2,3-dione	5.3	5	1	2
12	 [Fmoc-L-Norleucine][Fmoc-L-2-Naphthylalanine][m-Tolylacetic acid]	561.8	561.3	(5S)-1-((1S)-1-[(benzylamino)methyl]pentyl)-4-(2-(3-methylphenyl)ethyl)-5-(2-naphthylmethyl)piperazine-2,3-dione	4.7	5	1	2
13	 [Fmoc-D-Norleucine][Fmoc-D-Leucine][4-Isobutyl-alpha-Methylphenylacetic Acid]	533.8	533.4	(5R)-1-((1R)-1-[(benzylamino)methyl]pentyl)-5-isobutyl-4-[2-(4-isobutylphenyl)propyl]piperazine-2,3-dione	4.6	5	1	2
14	 [Fmoc-D-Norleucine][Fmoc-D-Leucine][3,5-Bis(Trifluoromethyl)-Phenylacetic Acid]	599.7	599.3	(5R)-1-((1R)-1-[(benzylamino)methyl]pentyl)-4-(2-[3,5-bis(trifluoromethyl)phenyl]ethyl)-5-isobutylpiperazine-2,3-dione	5.4	5	1	2
15	 [Fmoc-D-Norleucine][Fmoc-D-Leucine][Heptanoic acid]	457.7	457.4	(5R)-1-((1R)-1-[(benzylamino)methyl]pentyl)-4-heptyl-5-isobutylpiperazine-2,3-dione	3.7	5	1	0
16	 [Fmoc-D-Norleucine][Fmoc-D-Leucine][(Alpha-Alpha-Alpha-Trifluoro-m-Tolyl) acetic acid]	531.7	531.3	(5R)-1-((1R)-1-[(benzylamino)methyl]pentyl)-5-isobutyl-4-(2-[3-(trifluoromethyl)phenyl]ethyl)piperazine-2,3-dione	4.4	5	1	2
17	 [Fmoc-D-Norleucine][Fmoc-D-Leucine][4-tert-Butyl-cyclohexanecarboxylic acid]	511.8	511.4	(5R)-1-((1R)-1-[(benzylamino)methyl]pentyl)-4-[(4-tert-butylcyclohexyl)methyl]-5-isobutylpiperazine-2,3-dione	4.5	5	1	2
18	 [Fmoc-D-Norleucine][Fmoc-D-Leucine][m-Tolylacetic acid]	477.7	477.3	(5R)-1-((1R)-1-[(benzylamino)methyl]pentyl)-5-isobutyl-4-[2-(3-methylphenyl)ethyl]piperazine-2,3-dione	3.9	5	1	0

FIGURE 23A (cont.)

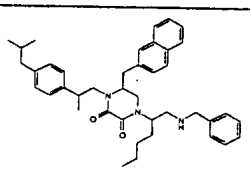
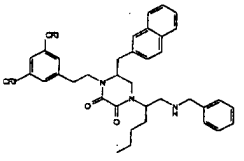
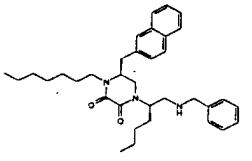
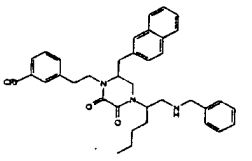
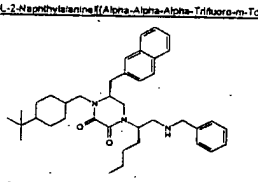
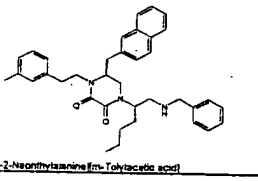
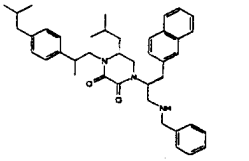
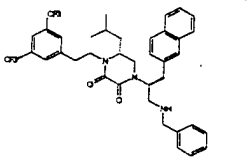
TPI1391	Structures FIGURE 23A	MW	Exact Mass	Name	MLogP	HBondDonor	HBondAcceptor	RuleOfFive
19	 [Fmoc-D-Norleucine][Fmoc-L-2-Naphthylalanine][4-Isobutyl-alpha-Methylphenylacetic Acid]	617.9	617.4	(5S)-1-[(1R)-1-[(benzylamino)methyl]pentyl]-4-[2-(4-isobutylphenyl)propyl]-5-(2-naphthylmethyl)piperazine-2,3-dione	5.4	5	1	2
20	 [Fmoc-D-Norleucine][Fmoc-L-2-Naphthylalanine][3,5-Bis(Trifluoromethyl)-Phenylacetic Acid]	683.7	683.3	(5S)-1-[(1R)-1-[(benzylamino)methyl]pentyl]-4-[2-[3,5-bis(trifluoromethyl)phenyl]ethyl]-5-(2-naphthylmethyl)piperazine-2,3-dione	6.2	5	1	2
21	 FALSE	541.8	541.4	(5S)-1-[(1R)-1-[(benzylamino)methyl]pentyl]-4-heptyl-5-(2-naphthylmethyl)piperazine-2,3-dione	4.6	5	1	2
22	 [Fmoc-D-Norleucine][Fmoc-L-2-Naphthylalanine][Alpha-Alpha-Alpha-Trifluoro-m-Tolyl) acetic acid]	615.7	615.3	(5S)-1-[(1R)-1-[(benzylamino)methyl]pentyl]-5-(2-naphthylmethyl)-4-[2-[3-(trifluoromethyl)phenyl]ethyl]piperazine-2,3-dione	5.3	5	1	2
23	 [Fmoc-D-Norleucine][Fmoc-L-2-Naphthylalanine][4-tert-Butyl-cyclohexanecarboxylic acid]	595.9	595.4	(5S)-1-[(1R)-1-[(benzylamino)methyl]pentyl]-4-[(4-tert-butylcyclohexyl)methyl]-5-(2-naphthylmethyl)piperazine-2,3-dione	5.3	5	1	2
24	 [Fmoc-D-Norleucine][Fmoc-L-2-Naphthylalanine][m-Tolylacetic acid]	561.8	561.3	(5S)-1-[(1R)-1-[(benzylamino)methyl]pentyl]-4-[2-(3-methylphenyl)ethyl]-5-(2-naphthylmethyl)piperazine-2,3-dione	4.7	5	1	2
25	 [Fmoc-L-2-Naphthylalanine][Fmoc-D-Leucine][4-Isobutyl-alpha-Methylphenylacetic Acid]	617.9	617.4	(5R)-1-[(1S)-2-(benzylamino)-1-(2-naphthylmethyl)ethyl]-5-isobutyl-4-[2-(4-isobutylphenyl)propyl]piperazine-2,3-dione	5.4	5	1	2
26	 [Fmoc-L-2-Naphthylalanine][Fmoc-D-Leucine][3,5-Bis(Trifluoromethyl)-Phenylacetic Acid]	683.7	683.3	(5R)-1-[(1S)-2-(benzylamino)-1-(2-naphthylmethyl)ethyl]-4-[2-[3,5-bis(trifluoromethyl)phenyl]ethyl]-5-isobutylpiperazine-2,3-dione	6.2	5	1	2
27	 [Fmoc-L-2-Naphthylalanine][Fmoc-D-Leucine][Heptanoic acid]	541.8	541.4	(5R)-1-[(1S)-2-(benzylamino)-1-(2-naphthylmethyl)ethyl]-4-heptyl-5-isobutylpiperazine-2,3-dione	4.6	5	1	2

FIGURE 23A (cont.)

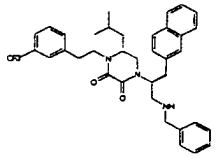
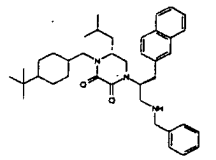
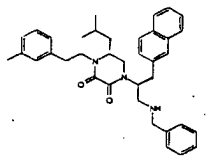
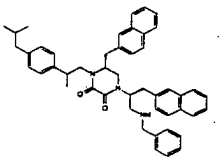
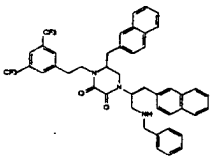
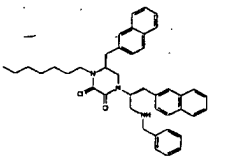
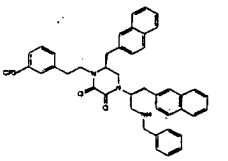
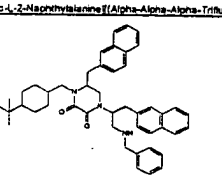
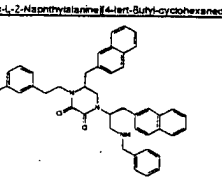
TPI1391	Structures FIGURE 23A	MW	Exact Mass	Name	* MLogP	HBondDonor	HBondDonor	RuleOfFive
28	 [Fmoc-L-2-Naphthylalanine][Fmoc-O-Leucine][(Alpha-Alpha-Alpha-Trifluoro-m-Tolyl) acetic acid]	515.7	515.3	(5R)-1-[(1S)-2-(benzylamino)-1-(2-naphthylmethyl)ethyl]-5-isobutyl-4-[2-[3-(trifluoromethyl)phenyl]ethyl]piperazine-2,3-dione	5.3	5	1	2
29	 [Fmoc-L-2-Naphthylalanine][Fmoc-O-Leucine][4-tert-Butyl-cyclohexanecarboxylic acid]	595.9	595.4	(5R)-1-[(1S)-2-(benzylamino)-1-(2-naphthylmethyl)ethyl]-4-[(4-tert-butylcyclohexyl)methyl]-5-isobutylpiperazine-2,3-dione	5.3	5	1	2
30	 [Fmoc-L-2-Naphthylalanine][Fmoc-O-Leucine][m-Tolylacetic acid]	561.8	561.3	(5R)-1-[(1S)-2-(benzylamino)-1-(2-naphthylmethyl)ethyl]-5-isobutyl-4-[2-(3-methylphenyl)ethyl]piperazine-2,3-dione	4.7	5	1	2
31	 [Fmoc-L-2-Naphthylalanine][Fmoc-L-2-Naphthylalanine][4-Isobutyl-alpha-Methylphenylacetic Acid]	702.0	701.4	(5S)-1-[(1S)-2-(benzylamino)-1-(2-naphthylmethyl)ethyl]-4-[2-(4-isobutylphenyl)propyl]-5-(2-naphthylmethyl)piperazine-2,3-dione	8.2	5	1	2
32	 [Fmoc-L-2-Naphthylalanine][Fmoc-L-2-Naphthylalanine][3,5-Bis(Trifluoromethyl)-Phenylacetic Acid]	787.8	787.3	(5S)-1-[(1S)-2-(benzylamino)-1-(2-naphthylmethyl)ethyl]-4-[2-[3,5-bis(trifluoromethyl)phenyl]ethyl]-5-(2-naphthylmethyl)piperazine-2,3-dione	7.0	5	1	2
33	 [Fmoc-L-2-Napnthylalanine][Fmoc-L-2-Napnthylalanine][Heptanoic acid]	625.9	625.4	(5S)-1-[(1S)-2-(benzylamino)-1-(2-naphthylmethyl)ethyl]-4-heptyl-5-(2-naphthylmethyl)piperazine-2,3-dione	5.4	5	1	2
34	 [Fmoc-L-2-Napnthylalanine][Fmoc-L-2-Naphthylalanine][(Alpha-Alpha-Alpha-Trifluoro-m-Tolyl) acetic acid]	699.8	699.3	(5S)-1-[(1S)-2-(benzylamino)-1-(2-naphthylmethyl)ethyl]-5-(2-naphthylmethyl)-4-(2-[3-(trifluoromethyl)phenyl]ethyl)piperazine-2,3-dione	6.1	5	1	2
35	 [Fmoc-L-2-Naphthylalanine][Fmoc-L-2-Napnthylalanine][4-tert-Butyl-cyclohexanecarboxylic acid]	679.9	679.4	(5S)-1-[(1S)-2-(benzylamino)-1-(2-naphthylmethyl)ethyl]-4-[(4-tert-butylcyclohexyl)methyl]-5-(2-naphthylmethyl)piperazine-2,3-dione	6.1	5	1	2
36	 [Fmoc-L-2-Naphthylalanine][Fmoc-L-2-Napnthylalanine][m-Tolylacetic acid]	645.8	645.3	(5S)-1-[(1S)-2-(benzylamino)-1-(2-naphthylmethyl)ethyl]-4-[2-(3-methylphenyl)ethyl]-5-(2-naphthylmethyl)piperazine-2,3-dione	5.6	5	1	2

FIGURE 23A (cont.)

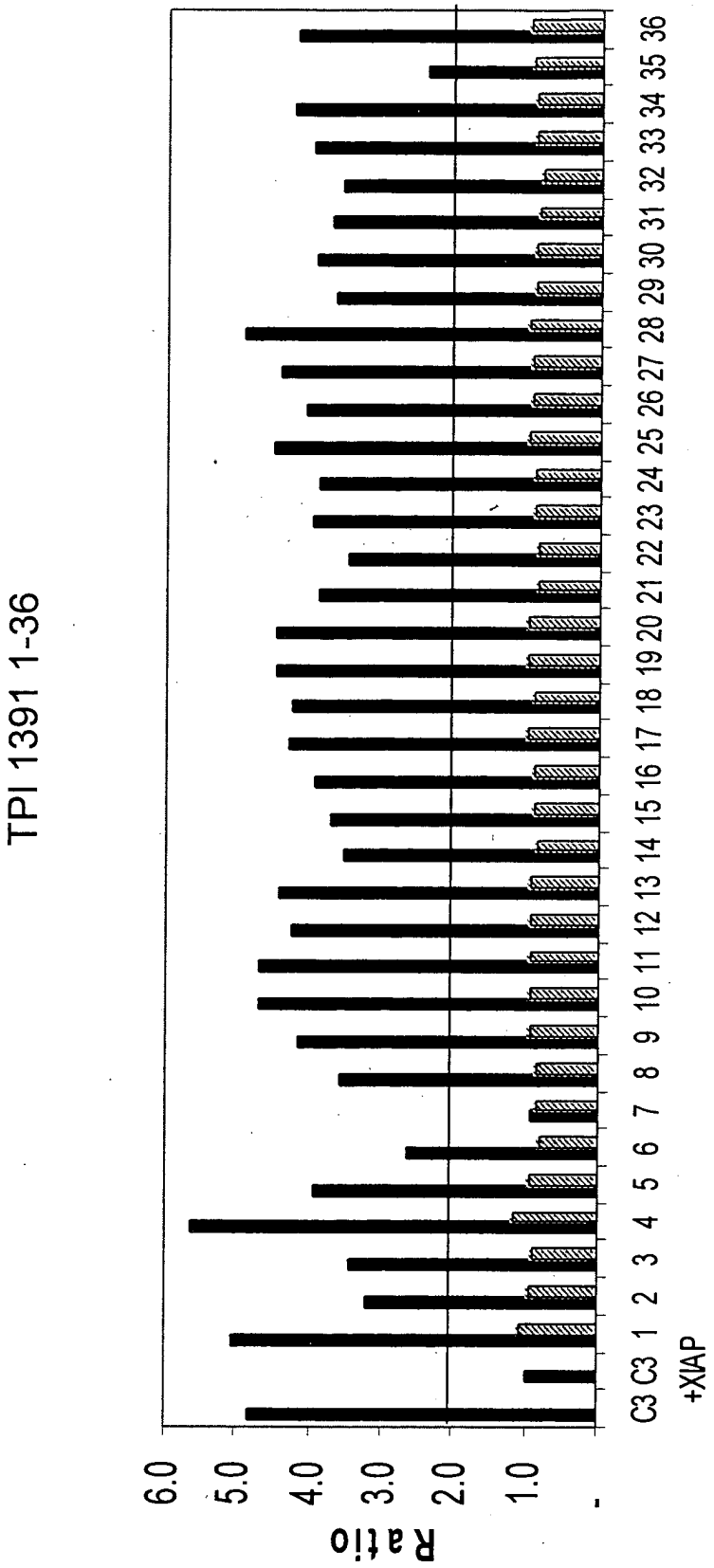

TPI 1391 1-36
Ratio
6.0
5.0
4.0
3.0
2.0
1.0
-
C3 C3 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36
+XIAP
Compound #
XIAP Caspase 3

FIGURE 23B

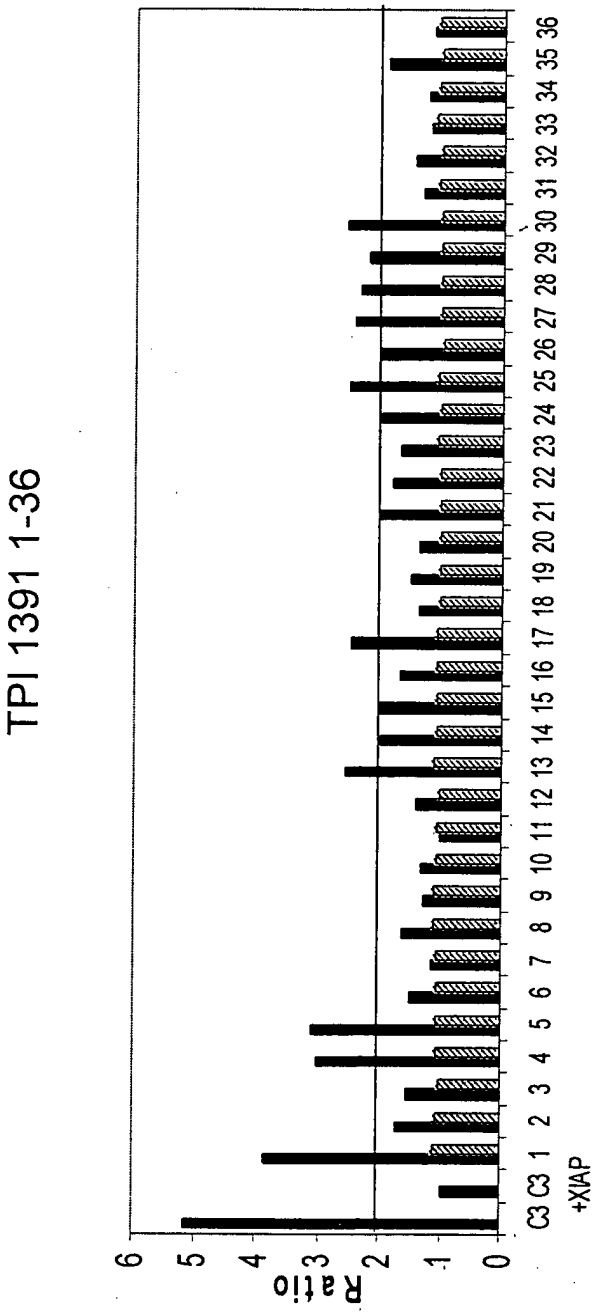

TPI 1391 1-36
Ratio
0
1
2
3
4
5
6
C3 C3 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36
+XIAP
Compound #
XIAP
Caspase 3

FIGURE 23C

Selected TPI 1391

TPI 1391	Caspase 3-XIAP IC-50 (μM)	
	AVG	STD
1	**29.6**	2.9
4	**28.0**	2.1
5	**29.9**	2.5
7	**>162**	
17	**57.3**	16.1
21	**33.6**	0.7
25	**29.0**	2.8
28	**25.1**	5.9
34	**39.4**	0.5
35	**32.6**	1.2

FIGURE 23D

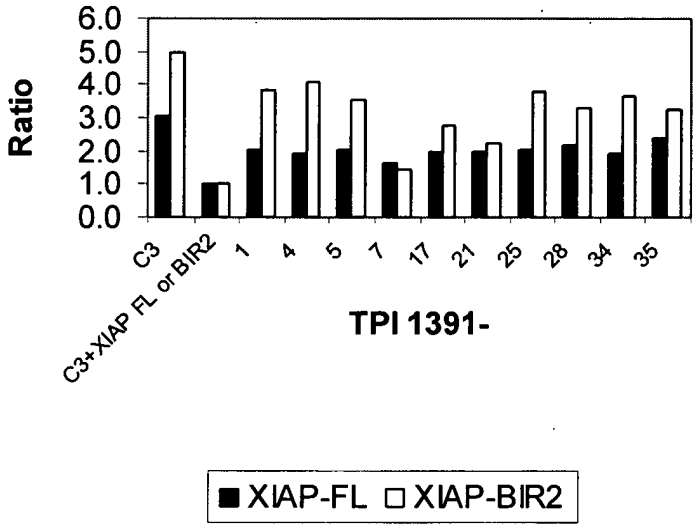

Ratio
6.0
5.0
4.0
3.0
2.0
1.0
0.0
C3
C3+XIAP FL or BIR2
1
4
5
7
17
21
25
28
34
35
TPI 1391-
XIAP-FL
XIAP-BIR2

FIGURE 23E

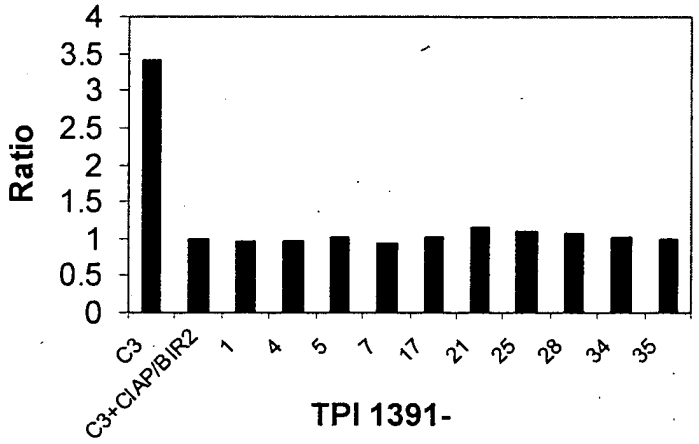

Ratio
4
3.5
3
2.5
2
1.5
1
0.5
0
C3
C3+CIAP/BIR2
1
4
5
7
17
21
25
28
34
35
TPI 1391-

FIGURE 23F

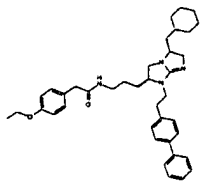
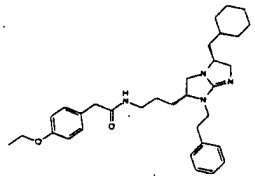
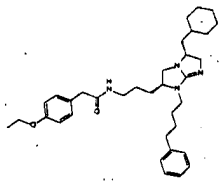
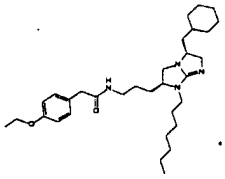
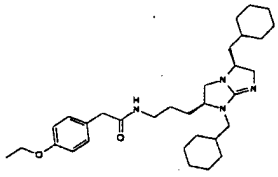
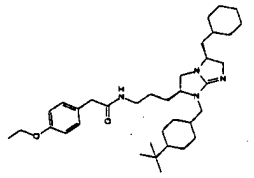
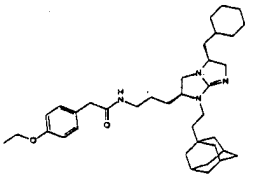
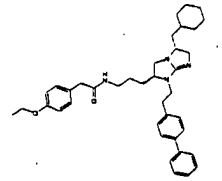
TPI1400	Structures FIGURE 24A	MW	Exact Mass	Name	MLogP	HBondAcceptor	HBondDonor	RuleOfFive
1	 [Boc-L-Cyclohexylalanine][4-Biphenylacetic acid][4-Ethoxyphenylacetic acid]	606.9	606.4	N-(3-{(2S,5S)-1-[2-(1,1'-biphenyl-4-yl)ethyl]-5-(cyclohexylmethyl)-2,3,5,8-tetrahydro-1H-imidazo[1,2-a]imidazol-2-yl}propyl)-2-(4-ethoxyphenyl)acetamide	5.8	6	1	2
2	 [Boc-L-Cyclohexylalanine][Phenylacetic acid][4-Ethoxyphenylacetic acid]	530.8	530.4	N-(3-{(2S,5S)-5-(cyclohexylmethyl)-1-(2-phenylethyl)-2,3,5,8-tetrahydro-1H-imidazo[1,2-a]imidazol-2-yl}propyl)-2-(4-ethoxyphenyl)acetamide	4.7	6	1	2
3	 [Boc-L-Cyclohexylalanine][4-Phenylbutyric acid][4-Ethoxyphenylacetic acid]	558.8	558.4	N-(3-{(2S,5S)-5-(cyclohexylmethyl)-1-(4-phenylbutyl)-2,3,5,8-tetrahydro-1H-imidazo[1,2-a]imidazol-2-yl}propyl)-2-(4-ethoxyphenyl)acetamide	5.1	6	1	2
4	 [Boc-L-Cyclohexylalanine][Heptanoic acid][4-Ethoxyphenylacetic acid]	524.8	524.4	N-(3-{(2S,5S)-5-(cyclohexylmethyl)-1-heptyl-2,3,5,8-tetrahydro-1H-imidazo[1,2-a]imidazol-2-yl}propyl)-2-(4-ethoxyphenyl)acetamide	4.8	6	1	2
5	 [Boc-L-Cyclohexylalanine][Cyclohexanecarboxylic acid][4-Ethoxyphenylacetic acid]	522.8	522.4	N-(3-{(2S,5S)-1,5-bis(cyclohexylmethyl)-2,3,5,8-tetrahydro-1H-imidazo[1,2-a]imidazol-2-yl}propyl)-2-(4-ethoxyphenyl)acetamide	4.8	6	1	2
6	 [Boc-L-Cyclohexylalanine][4-tert-Butyl-cyclohexanecarboxylic acid][4-Ethoxyphenylacetic acid]	578.9	578.5	N-(3-{(2S,5S)-1-[(4-tert-butylcyclohexyl)methyl]-5-(cyclohexylmethyl)-2,3,5,8-tetrahydro-1H-imidazo[1,2-a]imidazol-2-yl}propyl)-2-(4-ethoxyphenyl)acetamide	5.5	6	1	2
7	 [Boc-L-Cyclohexylalanine][1-Adamantaneacetic acid][4-Ethoxyphenylacetic acid]	588.9	588.4	N-(3-{(2S,5S)-1-[2-(1-adamantyl)ethyl]-5-(cyclohexylmethyl)-2,3,5,8-tetrahydro-1H-imidazo[1,2-a]imidazol-2-yl}propyl)-2-(4-ethoxyphenyl)acetamide	5.7	6	1	2
8	 [Boc-D-Cyclohexylalanine][4-Biphenylacetic acid][4-Ethoxyphenylacetic acid]	606.9	606.4	N-(3-{(2S,5R)-1-[2-(1,1'-biphenyl-4-yl)ethyl]-5-(cyclohexylmethyl)-2,3,5,8-tetrahydro-1H-imidazo[1,2-a]imidazol-2-yl}propyl)-2-(4-ethoxyphenyl)acetamide	5.8	6	1	2

FIGURE 24A

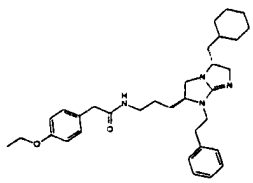
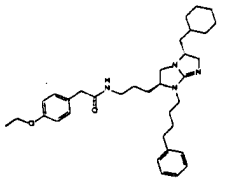
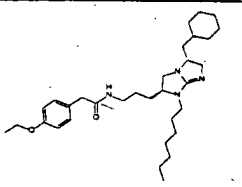
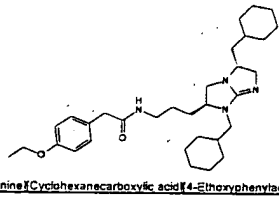
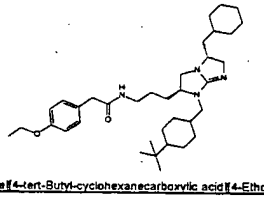
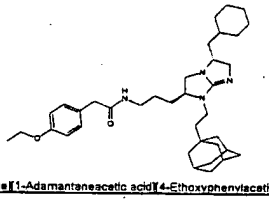
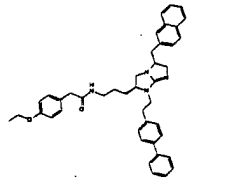
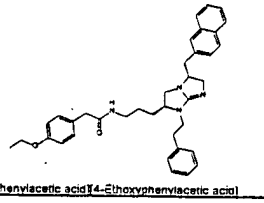
TPI1400	Structures FIGURE 24A	MW	Exact Mass	Name	MLogP	HBondAcceptor	HBondDonor	RuleOfFive
9	 [Boc-D-Cyclohexylalanine][Phenylacetic acid][4-Ethoxyphenylacetic acid]	530.8	530.4	N-(3-[(2S,5R)-5-(cyclohexylmethyl)-1-(2-phenylethyl)-2,3,5,8-tetrahydro-1H-imidazo[1,2-a]imidazol-2-yl]propyl)-2-(4-ethoxyphenyl)acetamide	4.7	6	1	2
10	 [Boc-D-Cyclohexylalanine][4-Phenylbutyric acid][4-Ethoxyphenylacetic acid]	558.8	558.4	N-(3-[(2S,5R)-5-(cyclohexylmethyl)-1-(4-phenylbutyl)-2,3,5,8-tetrahydro-1H-imidazo[1,2-a]imidazol-2-yl]propyl)-2-(4-ethoxyphenyl)acetamide	5.1	6	1	2
11	 [Boc-D-Cyclohexylalanine][Heptanoic acid][4-Ethoxyphenylacetic acid]	524.8	524.4	N-(3-[(2S,5R)-5-(cyclohexylmethyl)-1-heptyl-2,3,5,8-tetrahydro-1H-imidazo[1,2-a]imidazol-2-yl]propyl)-2-(4-ethoxyphenyl)acetamide	4.8	6	1	2
12	 [Boc-D-Cyclohexylalanine][Cyclohexanecarboxylic acid][4-Ethoxyphenylacetic acid]	522.8	522.4	N-(3-[(2S,5R)-1,5-bis(cyclohexylmethyl)-2,3,5,8-tetrahydro-1H-imidazo[1,2-a]imidazol-2-yl]propyl)-2-(4-ethoxyphenyl)acetamide	4.8	6	1	2
13	 [Boc-D-Cyclohexylalanine][4-tert-Butyl-cyclohexanecarboxylic acid][4-Ethoxyphenylacetic acid]	578.9	578.5	N-(3-[(2S,5R)-1-[(4-tert-butylcyclohexyl)methyl]-5-(cyclohexylmethyl)-2,3,5,8-tetrahydro-1H-imidazo[1,2-a]imidazol-2-yl]propyl)-2-(4-ethoxyphenyl)acetamide	5.5	6	1	2
14	 [Boc-D-Cyclohexylalanine][1-Adamantaneacetic acid][4-Ethoxyphenylacetic acid]	588.9	588.4	N-(3-[(2S,5R)-1-[2-(1-adamantyl)ethyl]-5-(cyclohexylmethyl)-2,3,5,8-tetrahydro-1H-imidazo[1,2-a]imidazol-2-yl]propyl)-2-(4-ethoxyphenyl)acetamide	5.7	6	1	2
15	 [Boc-L-Naphthylalanine][4-Biphenylacetic acid][4-Ethoxyphenylacetic acid]	650.9	650.4	N-(3-[(2S,5S)-1-[2-(1,1'-biphenyl-4-yl)ethyl]-5-(2-naphthylmethyl)-2,3,5,8-tetrahydro-1H-imidazo[1,2-a]imidazol-2-yl]propyl)-2-(4-ethoxyphenyl)acetamide	5.9	6	1	2
16	 [Boc-L-Naphthylalanine][Phenylacetic acid][4-Ethoxyphenylacetic acid]	574.8	574.3	2-(4-ethoxyphenyl)-N-(3-[(2S,5S)-5-(2-naphthylmethyl)-1-(2-phenylethyl)-2,3,5,8-tetrahydro-1H-imidazo[1,2-a]imidazol-2-yl]propyl)acetamide	5.1	6	1	2

FIGURE 24A (cont.)

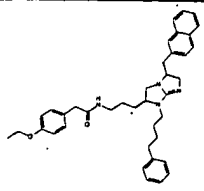
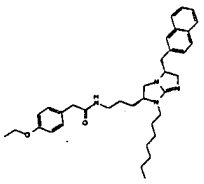
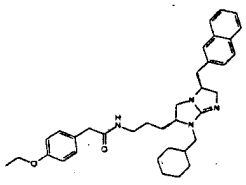
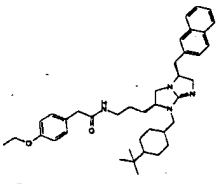
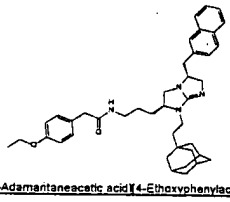
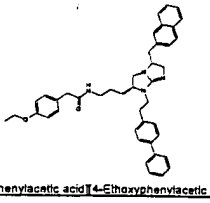
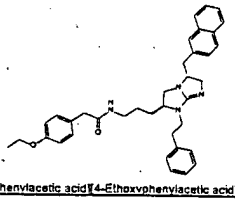
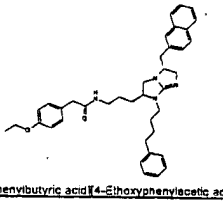
TPI1400	Structures FIGURE 24A	MW	Exact Mass	Name	MLogP	HBondAcceptor	HBondDonor	RuleOfFive
17	 [Boc-L-Naphthylalanine][4-Phenylbutyric acid][4-Ethoxyphenylacetic acid]	602.8	602.4	2-(4-ethoxyphenyl)-N-(3-[(2S,5S)-5-(2-naphthylmethyl)-1-(4-phenylbutyl)-2,3,5,8-tetrahydro-1H-imidazo[1,2-a]imidazol-2-yl]propyl)acetamide	5.4	6	1	2
18	 [Boc-L-Naphthylalanine][Heptanoic acid][4-Ethoxyphenylacetic acid]	568.8	568.4	2-(4-ethoxyphenyl)-N-(3-[(2S,5S)-1-heptyl-5-(2-naphthylmethyl)-2,3,5,8-tetrahydro-1H-imidazo[1,2-a]imidazol-2-yl]propyl)acetamide	5.1	6	1	2
19	 [Boc-L-Naphthylalanine][Cyclohexanecarboxylic acid][4-Ethoxyphenylacetic acid]	566.8	566.4	N-(3-[(2S,5S)-1-(cyclohexylmethyl)-5-(2-naphthylmethyl)-2,3,5,8-tetrahydro-1H-imidazo[1,2-a]imidazol-2-yl]propyl)-2-(4-ethoxyphenyl)acetamide	5.1	6	1	2
20	 [Boc-L-Naphthylalanine][4-tert-Butyl-cyclohexanecarboxylic acid][4-Ethoxyphenylacetic acid]	622.9	622.4	N-(3-[(2S,5S)-1-[(4-tert-butylcyclohexyl)methyl]-5-(2-naphthylmethyl)-2,3,5,8-tetrahydro-1H-imidazo[1,2-a]imidazol-2-yl]propyl)-2-(4-ethoxyphenyl)acetamide	5.8	6	1	2
21	 [Boc-L-Naphthylalanine][1-Adamantaneacetic acid][4-Ethoxyphenylacetic acid]	632.9	632.4	N-(3-[(2S,5S)-1-[2-(1-adamantyl)ethyl]-5-(2-naphthylmethyl)-2,3,5,8-tetrahydro-1H-imidazo[1,2-a]imidazol-2-yl]propyl)-2-(4-ethoxyphenyl)acetamide	6.0	6	1	2
22	 [Boc-O-Naphthylalanine][4-Biphenylacetic acid][4-Ethoxyphenylacetic acid]	650.9	650.4	N-(3-[(2S,5R)-1-[2-(1,1'-biphenyl-4-yl)ethyl]-5-(2-naphthylmethyl)-2,3,5,8-tetrahydro-1H-imidazo[1,2-a]imidazol-2-yl]propyl)-2-(4-ethoxyphenyl)acetamide	5.9	6	1	2
23	 [Boc-O-Naphthylalanine][Phenylacetic acid][4-Ethoxyphenylacetic acid]	574.8	574.3	2-(4-ethoxyphenyl)-N-(3-[(2S,5R)-5-(2-naphthylmethyl)-1-(2-phenylethyl)-2,3,5,8-tetrahydro-1H-imidazo[1,2-a]imidazol-2-yl]propyl)acetamide	5.1	6	1	2
24	 [Boc-O-Naphthylalanine][4-Phenylbutyric acid][4-Ethoxyphenylacetic acid]	602.8	602.4	2-(4-ethoxyphenyl)-N-(3-[(2S,5R)-5-(2-naphthylmethyl)-1-(4-phenylbutyl)-2,3,5,8-tetrahydro-1H-imidazo[1,2-a]imidazol-2-yl]propyl)acetamide	5.4	6	1	2

FIGURE 24A (cont.)

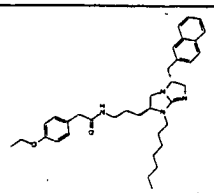
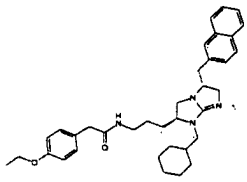
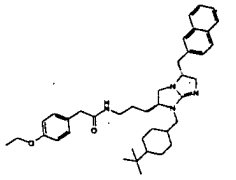
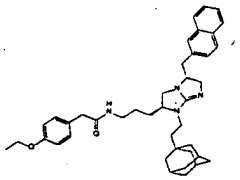
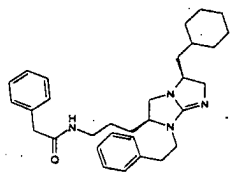
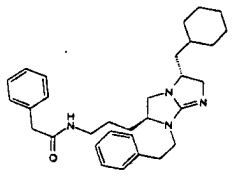
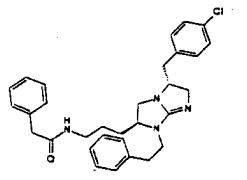
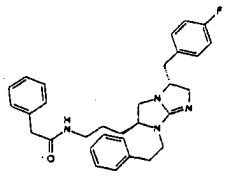
TPI1400	Structures FIGURE 24A	MW	Exact Mass	Name	MLogP	HBondAcceptor	HBondDonor	RuleOfFive
25	 [Boc-D-Naphthylalanine][Heptanoic acid][4-Ethoxyphenylacetic acid]	568.8	568.4	2-(4-ethoxyphenyl)-N-(3-[(2S,5R)-1-heptyl-5-(2-naphthylmethyl)-2,3,5,6-tetrahydro-1H-imidazo[1,2-a]imidazol-2-yl]propyl)acetamide	5.1	6	1	2
26	 [Boc-D-Naphthylalanine][Cyclohexanecarboxylic acid][4-Ethoxyphenylacetic acid]	568.8	568.4	N-(3-[(2S,5R)-1-(cyclohexylmethyl)-5-(2-naphthylmethyl)-2,3,5,6-tetrahydro-1H-imidazo[1,2-a]imidazol-2-yl]propyl)-2-(4-ethoxyphenyl)acetamide	5.1	6	1	2
27	 [Boc-D-Naphthylalanine][4-tert-Butyl-cyclohexanecarboxylic acid][4-Ethoxyphenylacetic acid]	622.9	622.4	N-(3-[(2S,5R)-1-[(4-tert-butylcyclohexyl)methyl]-5-(2-naphthylmethyl)-2,3,5,6-tetrahydro-1H-imidazo[1,2-a]imidazol-2-yl]propyl)-2-(4-ethoxyphenyl)acetamide	5.8	6	1	2
28	 [Boc-D-Naphthylalanine][1-Adamantaneacetic acid][4-Ethoxyphenylacetic acid]	632.9	632.4	N-(3-[(2S,5R)-1-[2-(1-adamantyl)ethyl]-5-(2-naphthylmethyl)-2,3,5,6-tetrahydro-1H-imidazo[1,2-a]imidazol-2-yl]propyl)-2-(4-ethoxyphenyl)acetamide	6.0	6	1	2
	Structures							
29	 [Boc-L-Cyclohexylalanine][Phenylacetic acid][Phenylacetic acid]	486.7	486.3	N-(3-[(2S,5S)-5-(cyclohexylmethyl)-1-(2-phenylethyl)-2,3,5,6-tetrahydro-1H-imidazo[1,2-a]imidazol-2-yl]propyl)-2-phenylacetamide	4.9	5	1	1
30	 [Boc-D-Cyclohexylalanine][Phenylacetic acid][Phenylacetic acid]	486.7	486.3	N-(3-[(2S,5R)-5-(cyclohexylmethyl)-1-(2-phenylethyl)-2,3,5,6-tetrahydro-1H-imidazo[1,2-a]imidazol-2-yl]propyl)-2-phenylacetamide	4.9	5	1	1
31	 [Boc-D-p-Chloro-Phenylalanine][Phenylacetic acid][Phenylacetic acid]	515.1	514.2	N-(3-[(2S,5R)-5-(4-chlorobenzyl)-1-(2-phenylethyl)-2,3,5,6-tetrahydro-1H-imidazo[1,2-a]imidazol-2-yl]propyl)-2-phenylacetamide	5.1	5	1	2
32	 [Boc-D-p-Fluoro-Phenylalanine][Phenylacetic acid][Phenylacetic acid]	498.6	498.3	N-(3-[(2S,5R)-5-(4-fluorobenzyl)-1-(2-phenylethyl)-2,3,5,6-tetrahydro-1H-imdazo[1,2-a]imidazol-2-yl]propyl)-2-phenylacetamide	5.0	5	1	1

FIGURE 24A (cont.)

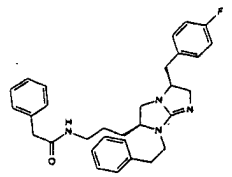
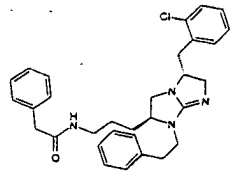
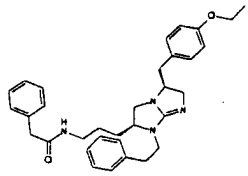
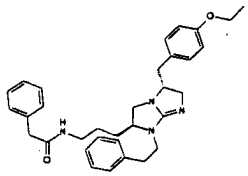
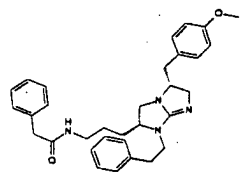
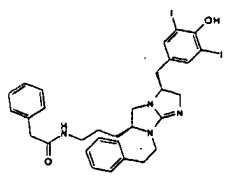
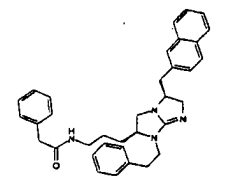
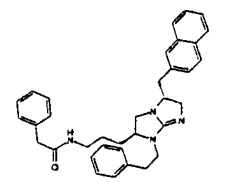
TPI1400	Structures FIGURE 24A	MW	Exact Mass	Name	MLogP	HBondAcceptor	HBondDonor	RuleOfFive
33	 [Boc-L-o-Fluoro-Phenylalanine][Phenylacetic acid][Phenylacetic acid]	498.6	498.3	N-{3-[(2S,5S)-5-(4-fluorobenzyl)-1-(2-phenylethyl)-2,3,5,6-tetrahydro-1H-imidazo[1,2-a]imidazol-2-yl]propyl}-2-phenylacetamide	5.0	5	1	1
34	 [Boc-O-2-Chloro-Phenylalanine][Phenylacetic acid][Phenylacetic acid]	515.1	514.2	N-{3-[(2S,5R)-5-(2-chlorobenzyl)-1-(2-phenylethyl)-2,3,5,6-tetrahydro-1H-imidazo[1,2-a]imidazol-2-yl]propyl}-2-phenylacetamide	5.1	5	1	2
35	 [Boc-L-O-Ethyl-Tyrosine][Phenylacetic acid][Phenylacetic acid]	524.7	524.3	N-{3-[(2S,5S)-5-(4-ethoxybenzyl)-1-(2-phenylethyl)-2,3,5,6-tetrahydro-1H-imidazo[1,2-a]imidazol-2-yl]propyl}-2-phenylacetamide	4.5	6	1	2
36	 [Boc-D-O-Ethyl-Tyrosine][Phenylacetic acid][Phenylacetic acid]	524.7	524.3	N-{3-[(2S,5R)-5-(4-ethoxybenzyl)-1-(2-phenylethyl)-2,3,5,6-tetrahydro-1H-imidazo[1,2-a]imidazol-2-yl]propyl}-2-phenylacetamide	4.5	6	1	2
37	 [Boc-D-O-Methyl-Tyrosine][Phenylacetic acid][Phenylacetic acid]	510.7	510.3	N-{3-[(2S,5R)-5-(4-methoxybenzyl)-1-(2-phenylethyl)-2,3,5,6-tetrahydro-1H-imidazo[1,2-a]imidazol-2-yl]propyl}-2-phenylacetamide	4.3	6	1	2
38	 [Boc-L-3,5-Diiodo-Tyrosine(BrZ)][Phenylacetic acid][Phenylacetic acid]	748.4	748.1	N-{3-[(2S,5S)-5-(4-hydroxy-3,5-diiodobenzyl)-1-(2-phenylethyl)-2,3,5,6-tetrahydro-1H-imidazo[1,2-a]imidazol-2-yl]propyl}-2-phenylacetamide	5.4	6	2	2
39	 [Boc-L-Naphthylalanine][Phenylacetic acid][Phenylacetic acid]	530.7	530.3	N-{3-[(2S,5S)-5-(2-naphthylmethyl)-1-(2-phenylethyl)-2,3,5,6-tetrahydro-1H-imidazo[1,2-a]imidazol-2-yl]propyl}-2-phenylacetamide	5.2	5	1	2
40	 [Boc-D-Naphthylalanine][Phenylacetic acid][Phenylacetic acid]	530.7	530.3	N-{3-[(2S,5R)-5-(2-naphthylmethyl)-1-(2-phenylethyl)-2,3,5,6-tetrahydro-1H-imidazo[1,2-a]imidazol-2-yl]propyl}-2-phenylacetamide	5.2	5	1	2

FIGURE 24A (cont.)

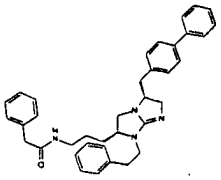
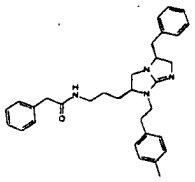
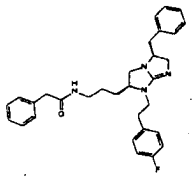
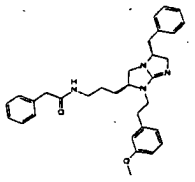
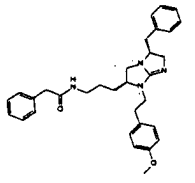
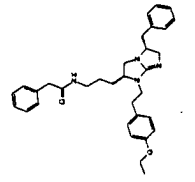
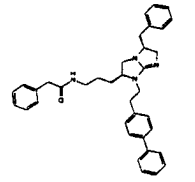
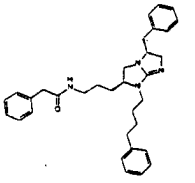
TPI1400	Structures FIGURE 24A	MW	Exact Mass	Name	MLogP	HBondAcceptor	HBondDonor	RuleOfFive
41	 [Boc-L-4,4'-Biphenyl-Alanine][Phenylacetic acid][Phenylacetic acid]	556.8	556.3	N-(3-[(2S,5S)-5-(1,1'-biphenyl-4-ylmethyl)-1-(2-phenylethyl)-2,3,5,6-tetrahydro-1H-imidazo[1,2-a]imidazol-2-yl]propyl)-2-phenylacetamide	5.5	5	1	2
	Structures							
42	 [Boc-L-Phenylalanine][p-Tolylacetic acid][Phenylacetic acid]	494.7	494.3	N-(3-[(2S,5S)-5-benzyl-1-[2-(4-methylphenyl)ethyl]-2,3,5,6-tetrahydro-1H-imidazo[1,2-a]imidazol-2-yl]propyl)-2-phenylacetamide	4.8	5	1	1
43	 [Boc-L-Phenylalanine][4-Fluorophenylacetic acid][Phenylacetic acid]	498.6	498.3	N-(3-[(2S,5S)-5-benzyl-1-[2-(4-fluorophenyl)ethyl]-2,3,5,6-tetrahydro-1H-imidazo[1,2-a]imidazol-2-yl]propyl)-2-phenylacetamide	5.0	5	1	1
44	 [Boc-L-Phenylalanine][3-Methoxyphenylacetic acid][Phenylacetic acid]	510.7	510.3	N-(3-[(2S,5S)-5-benzyl-1-[2-(3-methoxyphenyl)ethyl]-2,3,5,6-tetrahydro-1H-imidazo[1,2-a]imidazol-2-yl]propyl)-2-phenylacetamide	4.3	6	1	2
45	 [Boc-L-Phenylalanine][4-Methoxyphenylacetic acid][Phenylacetic acid]	510.7	510.3	N-(3-[(2S,5S)-5-benzyl-1-[2-(4-methoxyphenyl)ethyl]-2,3,5,6-tetrahydro-1H-imidazo[1,2-a]imidazol-2-yl]propyl)-2-phenylacetamide	4.3	6	1	2
46	 [Boc-L-Phenylalanine][4-Ethoxyphenylacetic acid][Phenylacetic acid]	524.7	524.3	N-(3-[(2S,5S)-5-benzyl-1-[2-(4-ethoxyphenyl)ethyl]-2,3,5,6-tetrahydro-1H-imidazo[1,2-a]imidazol-2-yl]propyl)-2-phenylacetamide	4.5	6	1	2
47	 [Boc-L-Phenylalanine][4-Biphenylacetic acid][Phenylacetic acid]	556.8	556.3	N-(3-[(2S,5S)-5-benzyl-1-[2-(1,1'-biphenyl-4-yl)ethyl]-2,3,5,6-tetrahydro-1H-imidazo[1,2-a]imidazol-2-yl]propyl)-2-phenylacetamide	5.5	5	1	2
48	 [Boc-L-Phenylalanine][4-Phenylbutyric acid][Phenylacetic acid]	508.7	508.3	N-(3-[(2S,5S)-5-benzyl-1-(4-phenylbutyl)-2,3,5,6-tetrahydro-1H-imidazo[1,2-a]imidazol-2-yl]propyl)-2-phenylacetamide	5.0	5	1	2

FIGURE 24A (cont.)

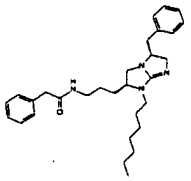
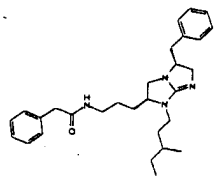
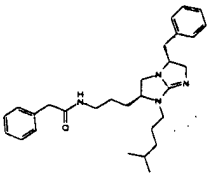
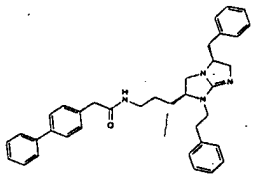
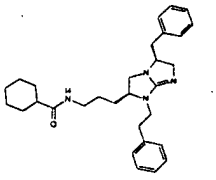
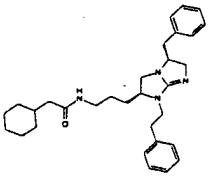
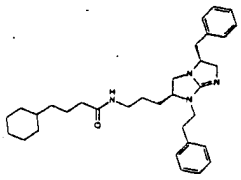
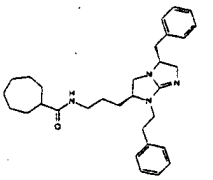
TPI1400	Structures FIGURE 24A	MW	Exact Mass	Name	MLogP	HBondAcceptor	HBondDonor	RuleOfFive
49	 [Boc-L-Phenylalanine][Heptanoic acid][Phenylacetic acid]	474.7	474.3	N-(3-[(2S,5S)-5-benzyl-1-heptyl-2,3,5,6-tetrahydro-1H-imidazo[1,2-a]imidazol-2-yl]propyl)-2-phenylacetamide	4.7	5	1	1
50	 [Boc-L-Phenylalanine][3-Methylvaleric acid][Phenylacetic acid]	460.7	460.3	N-(3-[(2S,5S)-5-benzyl-1-(3-methylpentyl)-2,3,5,6-tetrahydro-1H-imidazo[1,2-a]imidazol-2-yl]propyl)-2-phenylacetamide	4.5	5	1	1
51	 [Boc-L-Phenylalanine][4-Methylvaleric acid][Phenylacetic acid]	460.7	460.3	N-(3-[(2S,5S)-5-benzyl-1-(4-methylpentyl)-2,3,5,6-tetrahydro-1H-imidazo[1,2-a]imidazol-2-yl]propyl)-2-phenylacetamide	4.5	5	1	1
	Structures							
52	 [Boc-L-Phenylalanine][Phenylacetic acid][4-Biphenylacetic acid]	556.8	556.3	N-(3-[(2S,5S)-5-benzyl-1-(2-phenylethyl)-2,3,5,6-tetrahydro-1H-imidazo[1,2-a]imidazol-2-yl]propyl)-2-(1,1'-biphenyl-4-yl)acetamide	5.5	5	1	2
53	 [Boc-L-Phenylalanine][Phenylacetic acid][Cyclohexanecarboxylic acid]	472.7	472.3	N-(3-[(2S,5S)-5-benzyl-1-(2-phenylethyl)-2,3,5,6-tetrahydro-1H-imidazo[1,2-a]imidazol-2-yl]propyl)cyclohexanecarboxamide	4.7	5	1	1
54	 [Boc-L-Phenylalanine][Phenylacetic acid][Cyclohexaneacetic acid]	486.7	486.3	N-(3-[(2S,5S)-5-benzyl-1-(2-phenylethyl)-2,3,5,6-tetrahydro-1H-imidazo[1,2-a]imidazol-2-yl]propyl)-2-cyclohexylacetamide	4.9	5	1	1
55	 [Boc-L-Phenylalanine][Phenylacetic acid][Cyclohexanebutyric acid]	514.8	514.4	N-(3-[(2S,5S)-5-benzyl-1-(2-phenylethyl)-2,3,5,6-tetrahydro-1H-imidazo[1,2-a]imidazol-2-yl]propyl)-4-cyclohexylbutanamide	5.2	5	1	2
56	 [Boc-L-Phenylalanine][Phenylacetic acid][Cycloheptanecarboxylic acid]	486.7	486.3	N-(3-[(2S,5S)-5-benzyl-1-(2-phenylethyl)-2,3,5,6-tetrahydro-1H-imidazo[1,2-a]imidazol-2-yl]propyl)cycloheptanecarboxamide	4.9	5	1	1

FIGURE 24A (cont.)

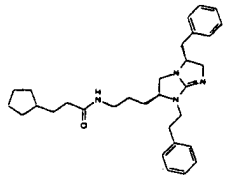
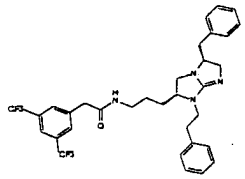
TPI1400	Structures FIGURE 24A	MW	Exact Mass	Name	MLogP	HBondAcceptor	HBondDonor	RuleOfFive
57	 [Boc-L-Phenylalanine][Phenylacetic acid][3-Cyclopentylpropionic acid]	486.7	486.3	N-(3-((2S,5S)-5-benzyl-1-(2-phenylethyl)-2,3,5,6-tetrahydro-1H-imidazo[1,2-a]imidazol-2-yl)propyl)-3-cyclopentylpropanamide	4.9	5	1	1
58	 [Boc-L-Phenylalanine][Phenylacetic acid][3,5-bis-(Trifluoromethyl)-phenylacetic acid]	616.6	616.3	N-(3-((2S,5S)-5-benzyl-1-(2-phenylethyl)-2,3,5,6-tetrahydro-1H-imidazo[1,2-a]imidazol-2-yl)propyl)-2-[3,5-bis(trifluoromethyl)phenyl]acetamide	6.4	5	1	2

FIGURE 24A (cont.)

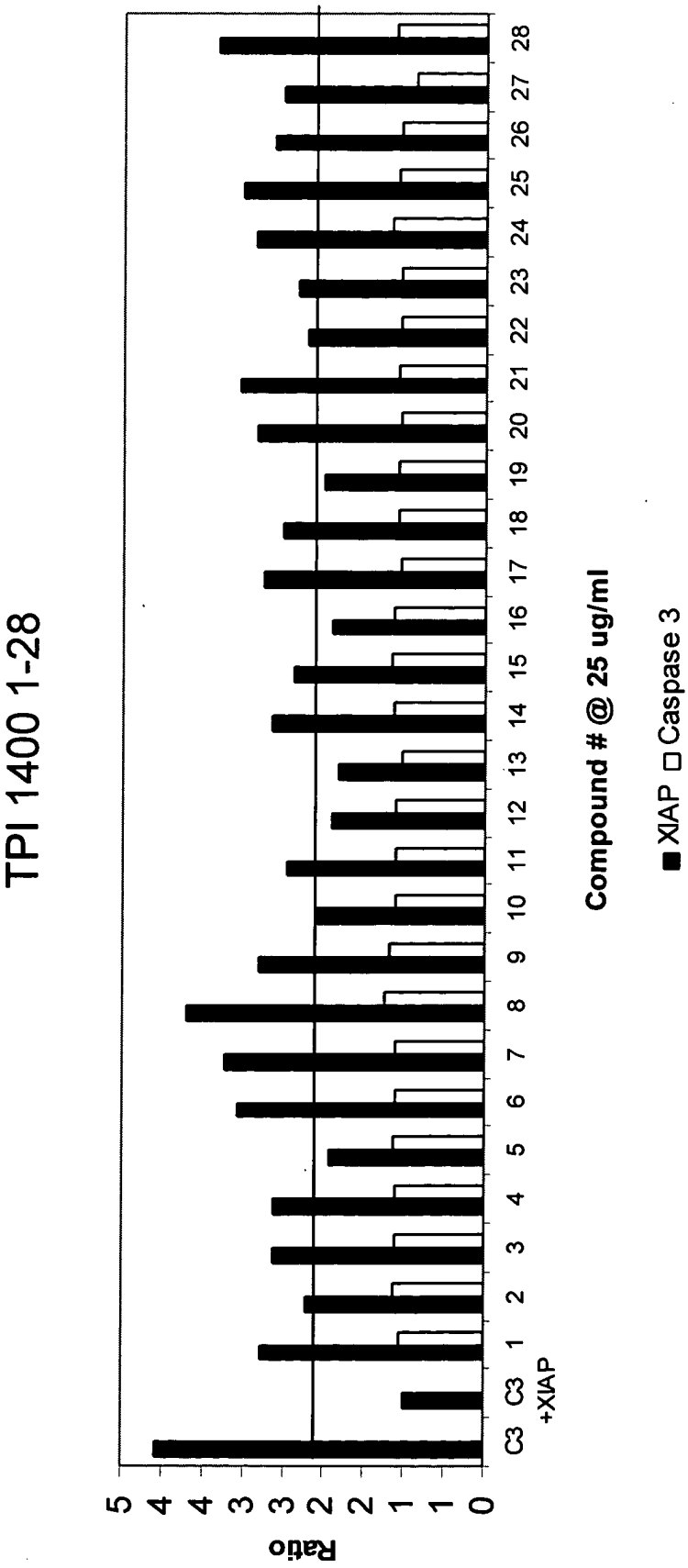

TPI 1400 1-28
Ratio
0
1
1
2
2
3
3
4
4
5
C3
C3 +XIAP
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
Compound # @ 25 ug/ml
XIAP
Caspase 3

FIGURE 24B

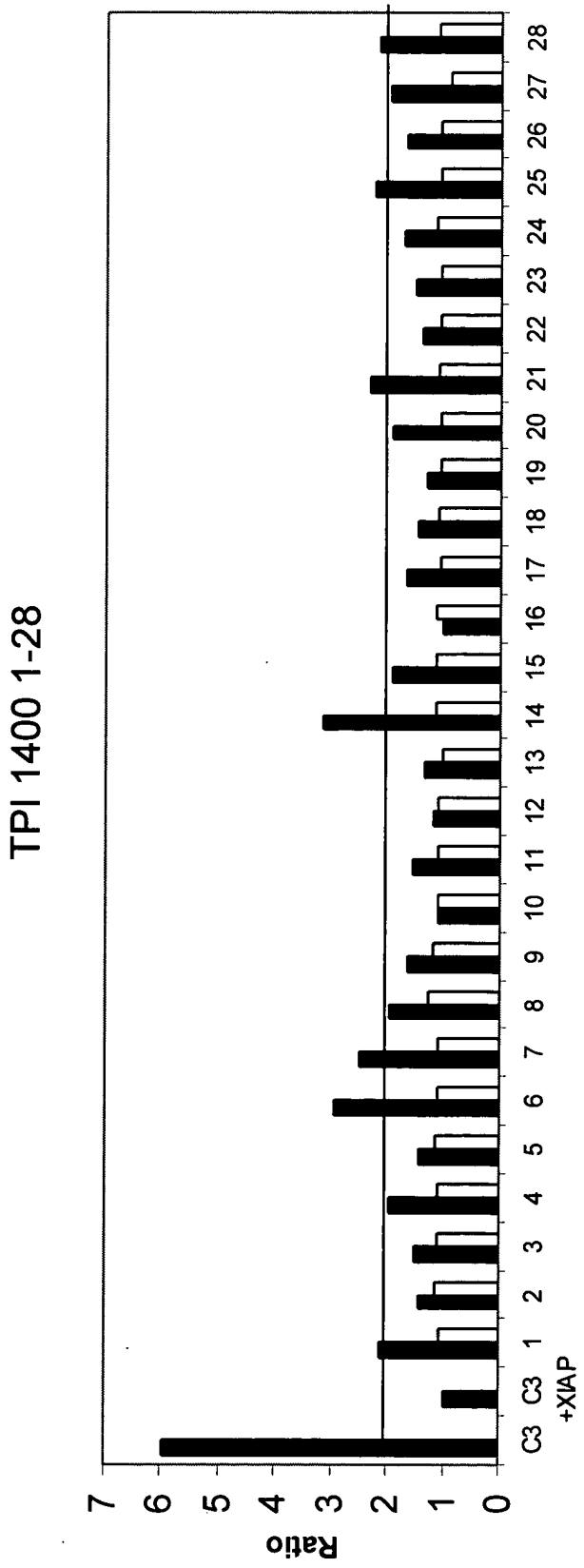

TPI 1400 1-28
Ratio
0
1
2
3
4
5
6
7
C3
C3 +XIAP
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
Compound # @ 10 ug/ml
XIAP
Caspase 3

FIGURE 24C

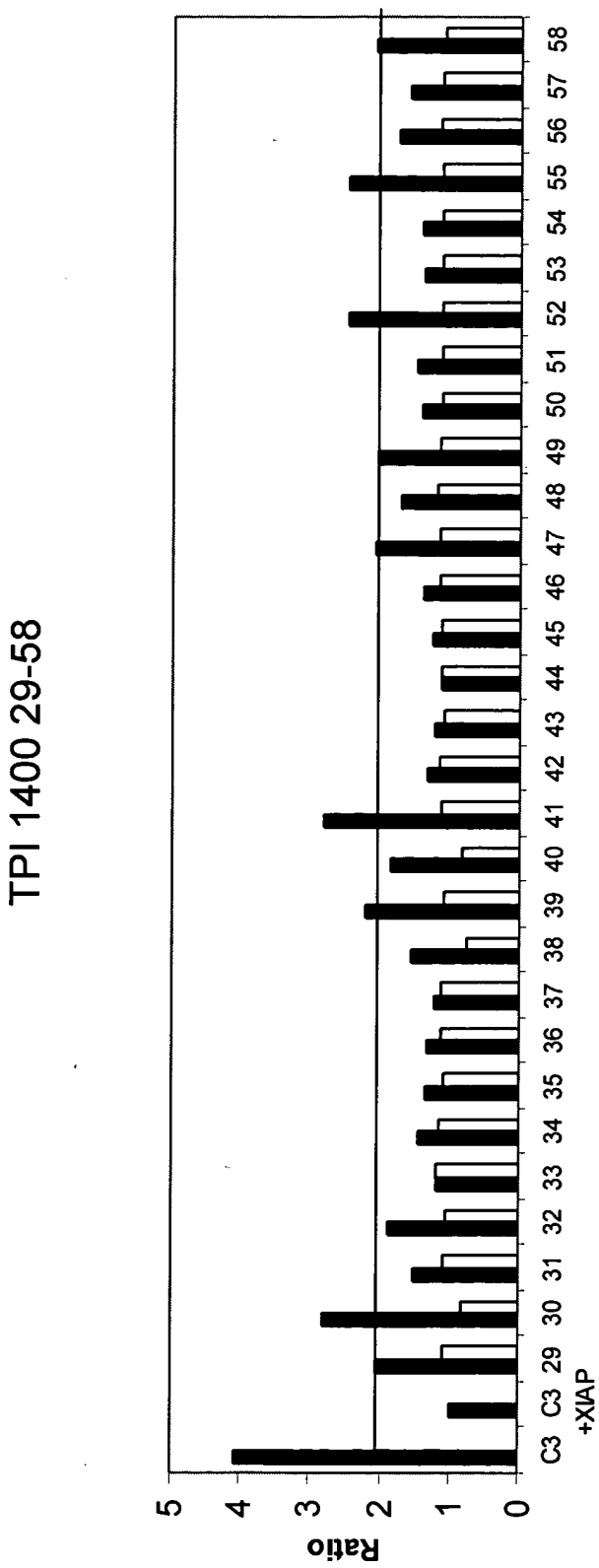

TPI 1400 29-58
Ratio
5
4
3
2
1
0
C3
C3 +XIAP
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
Compound # @ 25ug/ml
XIAP
Caspase 3

FIGURE 24D

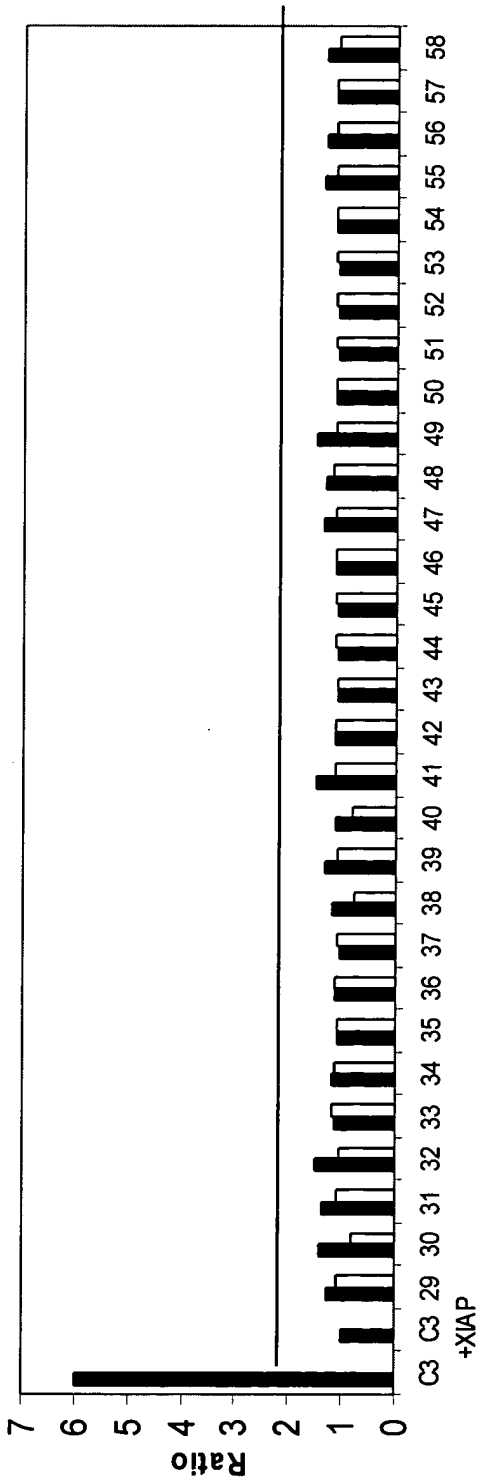

Ratio
7
6
5
4
3
2
1
0
C3
C3 +XIAP
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
Compound # @ 10ug/ml
XIAP
Caspase 3

FIGURE 24E

Selected TPI 1400

TPI 1400-	Caspase 3-XIAP IC-50 (μM)	
	AVG	STD
6	26.6	4.6
7	40.2	8.7
14	31.2	6.8
13	157.2	
33	>200	
37	157.6	
43	169.5	
44	120.2	

FIGURE 24F

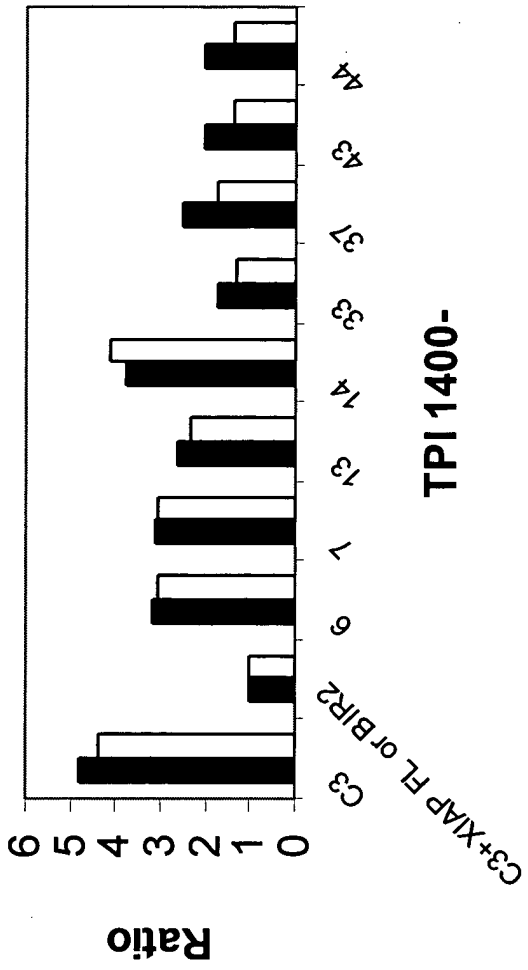
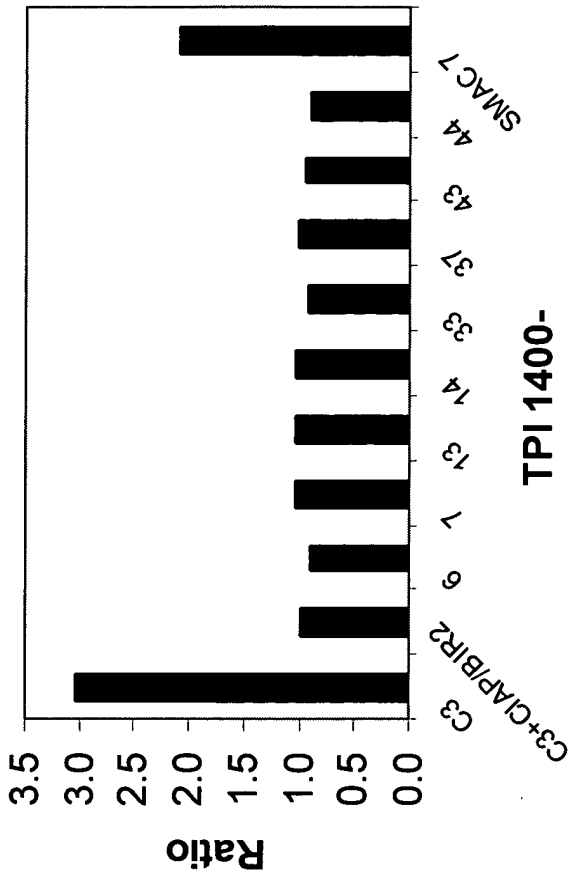

Ratio
0
1
2
3
4
5
6
C3
C3+XIAP FL or BIR2
6
7
13
14
33
37
43
44
TPI 1400-
XIAP-FL
XIAP-BIR2

FIGURE 24G



TPI 1400-

100 µg/ml 10, 2003

FIGURE 24H

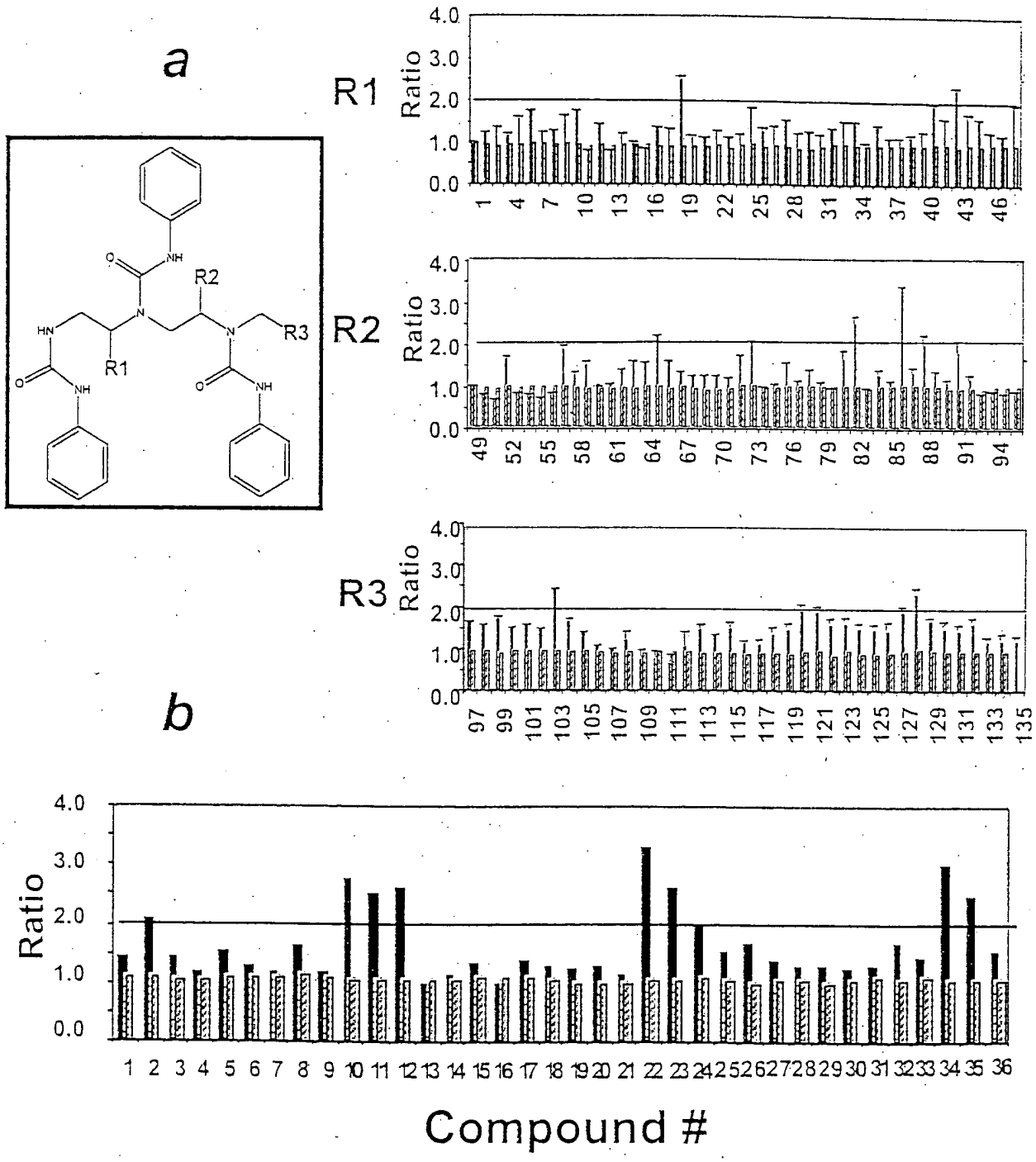


FIGURE 25

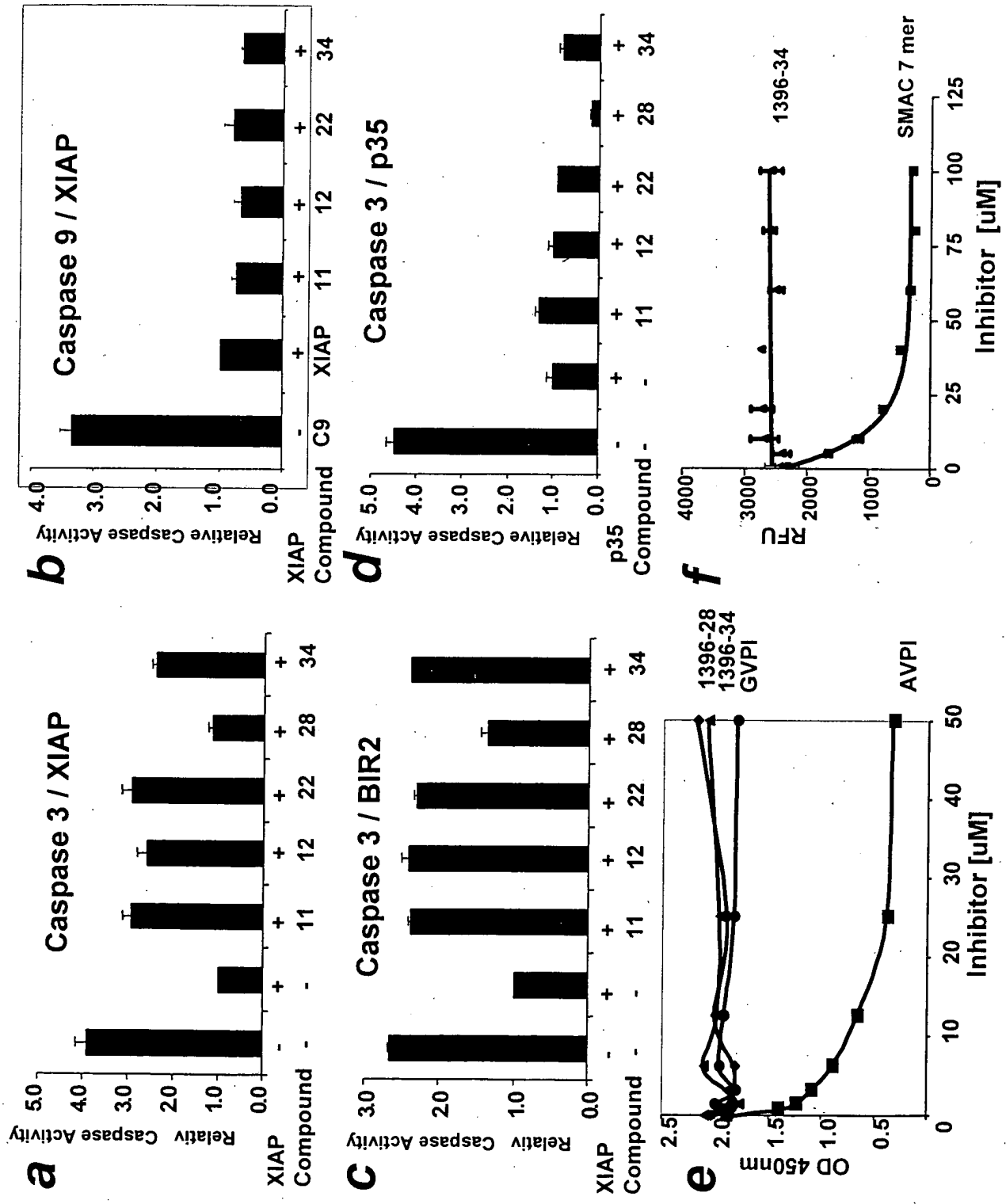

a
Caspase 3 / XIAP
Relativ Caspase Activity
5.0
4.0
3.0
2.0
1.0
0.0
XIAP
Compound - - + + + + + +
- 11 12 22 28 34
b
Caspase 9 / XIAP
Relative Caspase Activity
4.0
3.0
2.0
1.0
0.0
XIAP
Compound C9 XIAP + + + + + +
- 11 12 22 34
c
Caspase 3 / BIR2
Relativ Caspase Activity
3.0
2.0
1.0
0.0
XIAP
Compound - - + + + + + +
- 11 12 22 28 34
d
Caspase 3 / p35
Relative Caspase Activity
5.0
4.0
3.0
2.0
1.0
0.0
p35
Compound - - + + + + + +
- 11 12 22 28 34
e
OD 450nm
2.5
2.0
1.5
1.0
0.5
1396-28
1396-34
GVPI
AVPI
0
10
20
30
40
50
Inhibitor [uM]
f
RFU
4000
3000
2000
1000
0
1396-34
SMAC 7 mer
0
25
50
75
100
125
Inhibitor [uM]

FIGURE 26

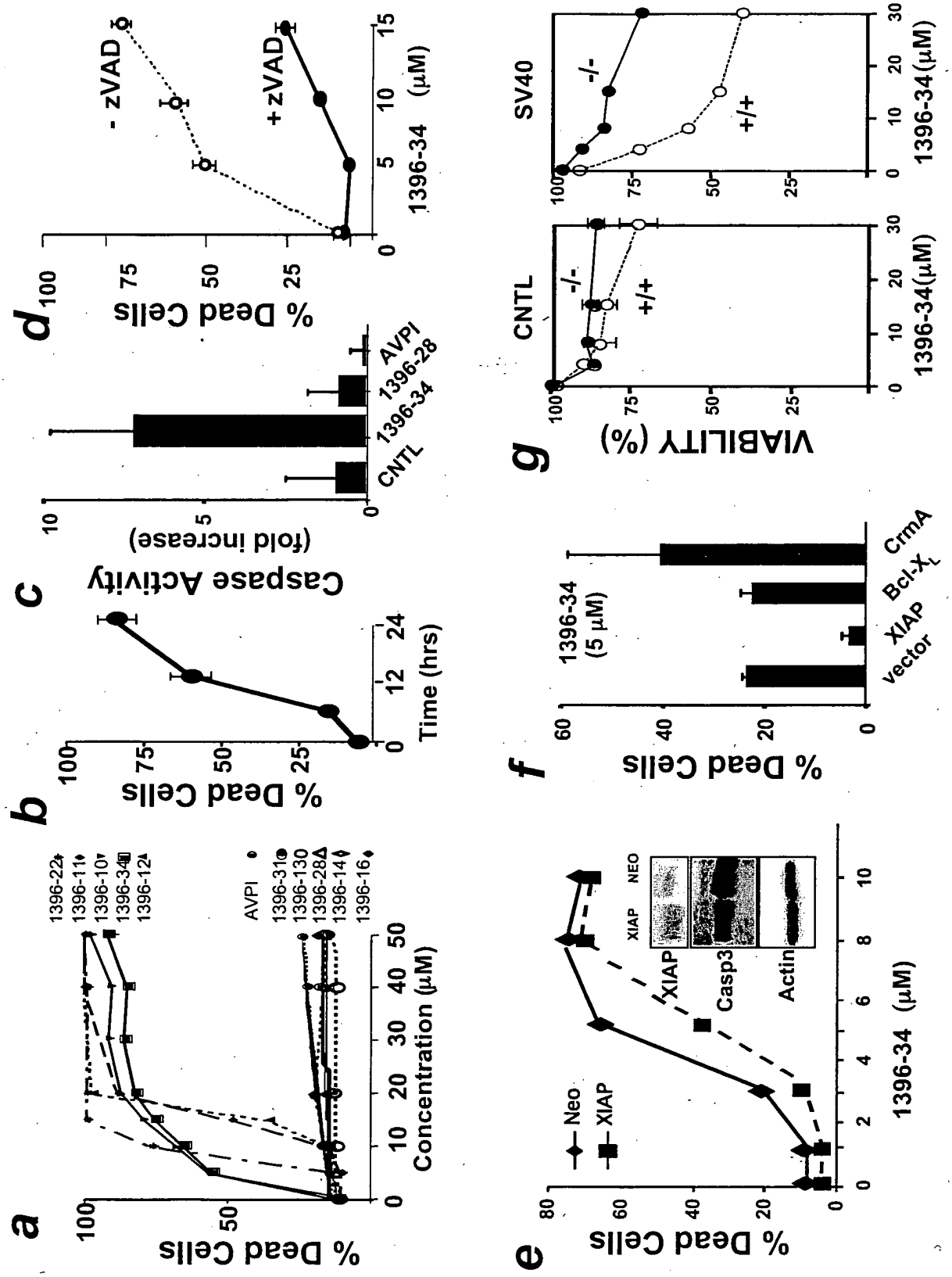

a
% Dead Cells
Concentration (μM)
1396-22
1396-11
1396-10
1396-34
1396-12
AVPI
1396-31
1396-130
1396-28
1396-14
1396-16
b
% Dead Cells
Time (hrs)
c
Caspase Activity
(fold increase)
CNTL
1396-34
1396-28
AVPI
d
% Dead Cells
- zVAD
+ zVAD
1396-34 (μM)
e
% Dead Cells
Neo
XIAP
1396-34 (μM)
XIAP
Casp3
Actin
NEO
f
% Dead Cells
1396-34 (5 μM)
vector
XIAP
Bcl-Xl
CrmA
g
VIABILITY (%)
CNTL
SV40
-/-
+/+
1396-34(μM)

FIGURE 27

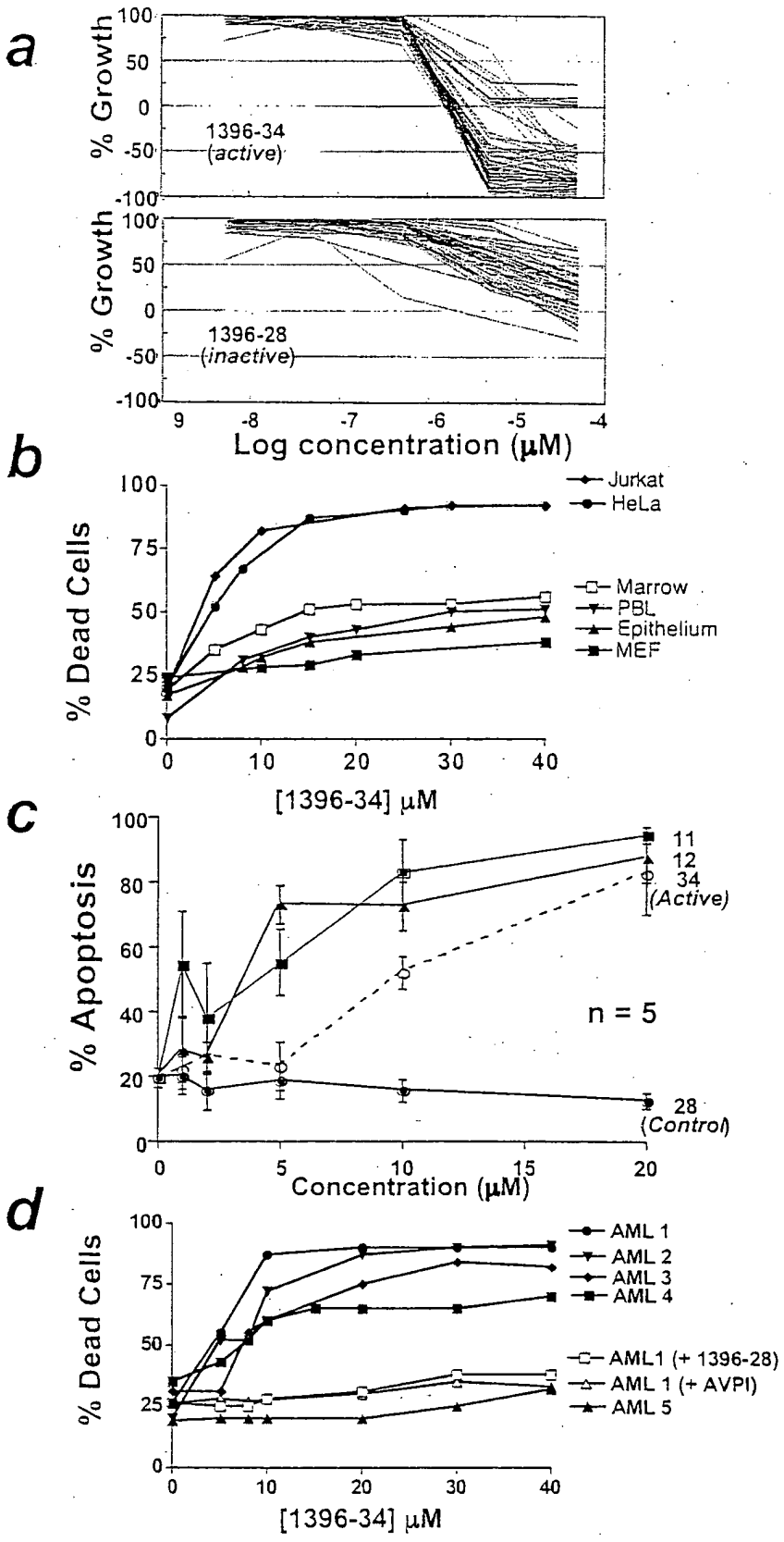

a
% Growth
100
50
0
-50
-100
1396-34
(active)
% Growth
1396-28
(inactive)
9
-8
-7
-6
-5
-4
Log concentration (μM)
b
% Dead Cells
100
75
50
25
0
0
10
20
30
40
[1396-34] μM
Jurkat
HeLa
Marrow
PBL
Epithelium
MEF
c
% Apoptosis
100
80
60
40
20
0
0
5
10
15
20
Concentration (μM)
11
12
34
(Active)
n = 5
28
(Control)
d
% Dead Cells
100
75
50
25
0
0
10
20
30
40
[1396-34] μM
AML 1
AML 2
AML 3
AML 4
AML1 (+ 1396-28)
AML 1 (+ AVPI)
AML 5

FIGURE 28

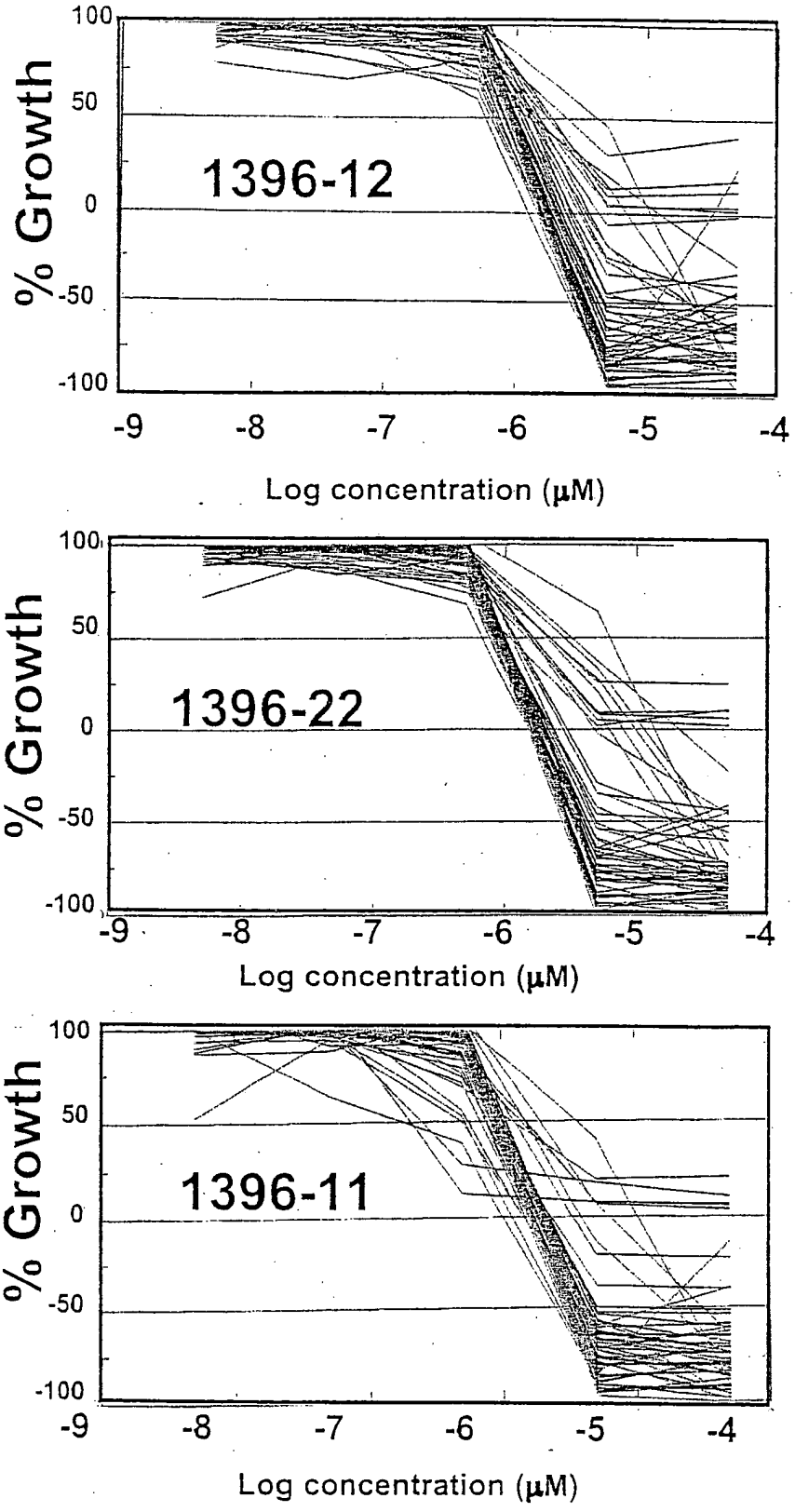

100
50
0
-50
-100
% Growth
1396-12
-9
-8
-7
-6
-5
-4
Log concentration (μM)
100
50
0
-50
-100
% Growth
1396-22
-9
-8
-7
-6
-5
-4
Log concentration (μM)
100
50
0
-50
-100
% Growth
1396-11
-9
-8
-7
-6
-5
-4
Log concentration (μM)

FIGURE 29

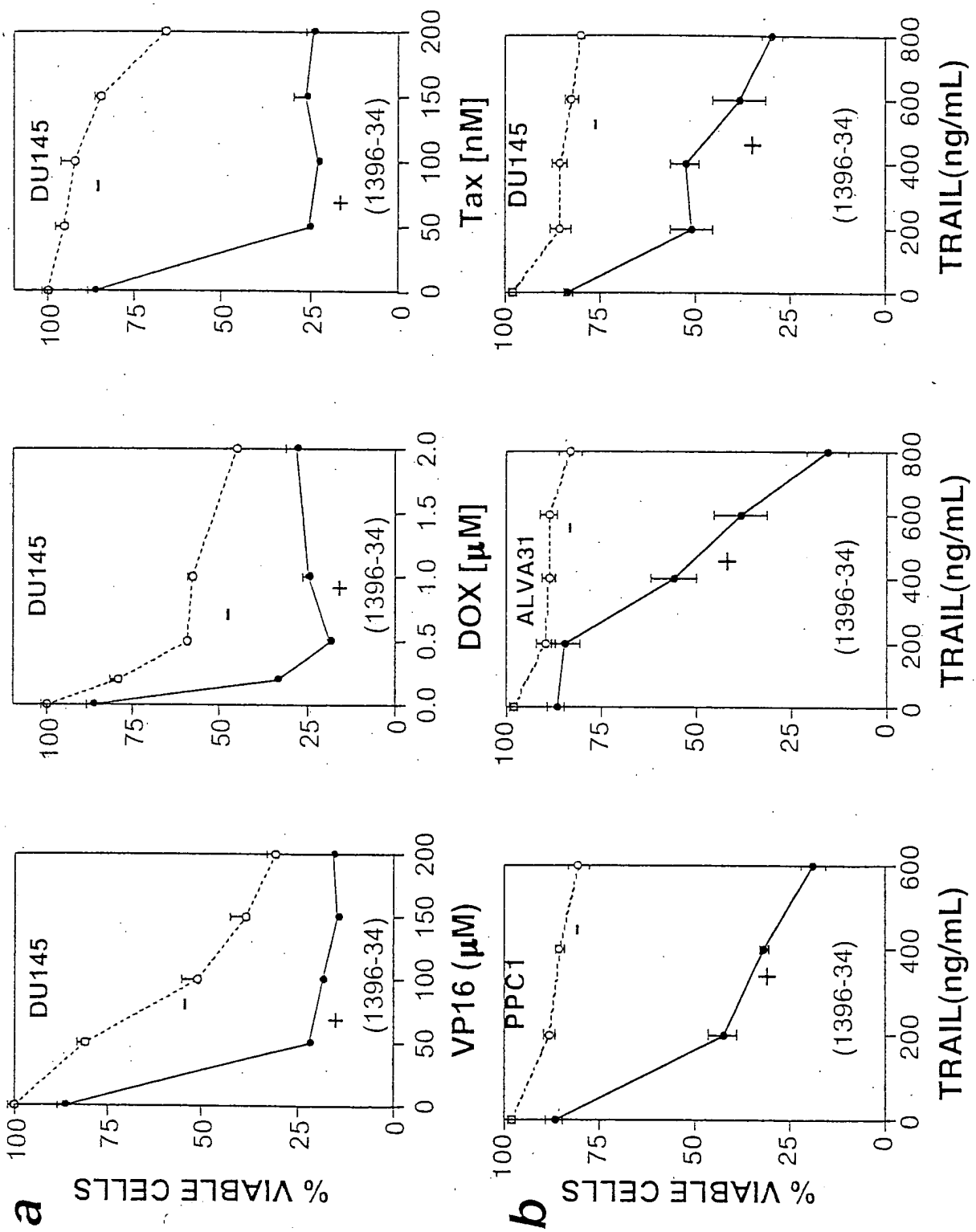

a
b
% VIABLE CELLS
VP16 (μM)
DOX [μM]
Tax [nM]
TRAIL(ng/mL)
DU145
PPC1
ALVA31
(1396-34)
+
-

FIGURE 30

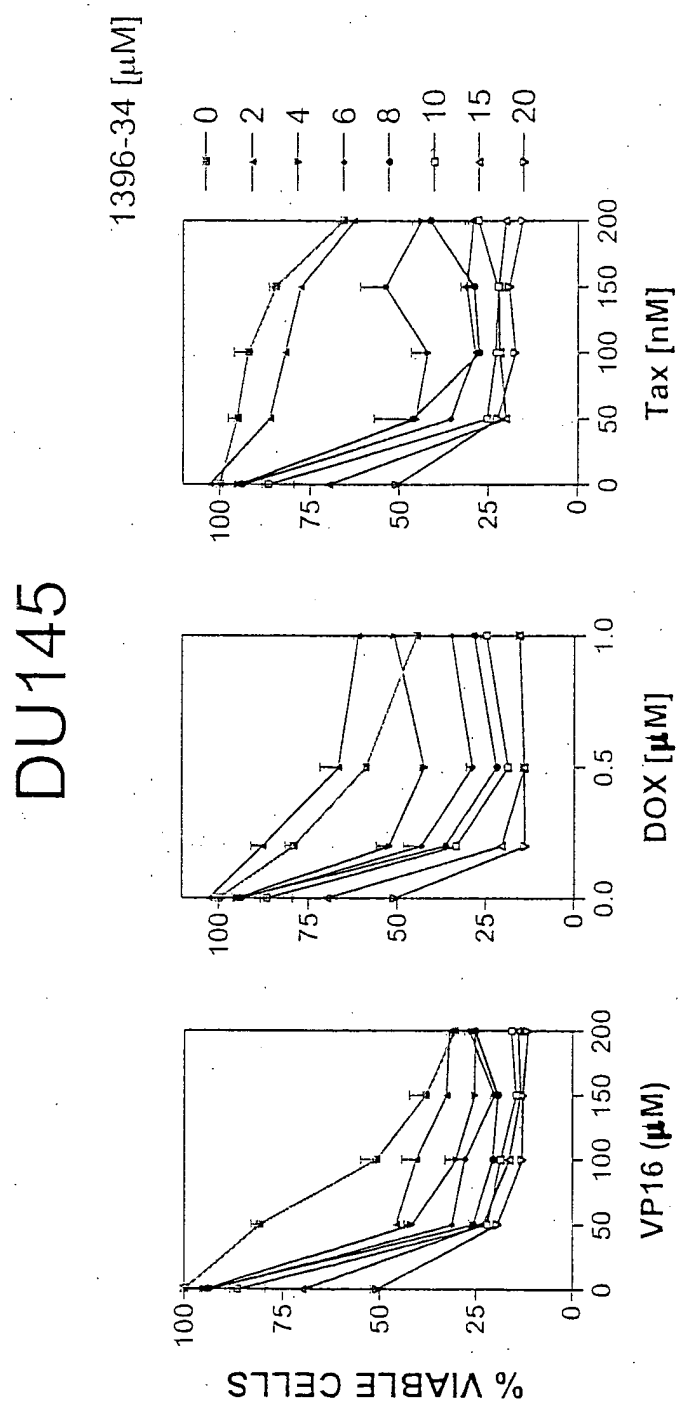

DU145
% VIABLE CELLS
VP16 (μM)
DOX [μM]
Tax [nM]
1396-34 [μM]
0
2
4
6
8
10
15
20

FIGURE 31A

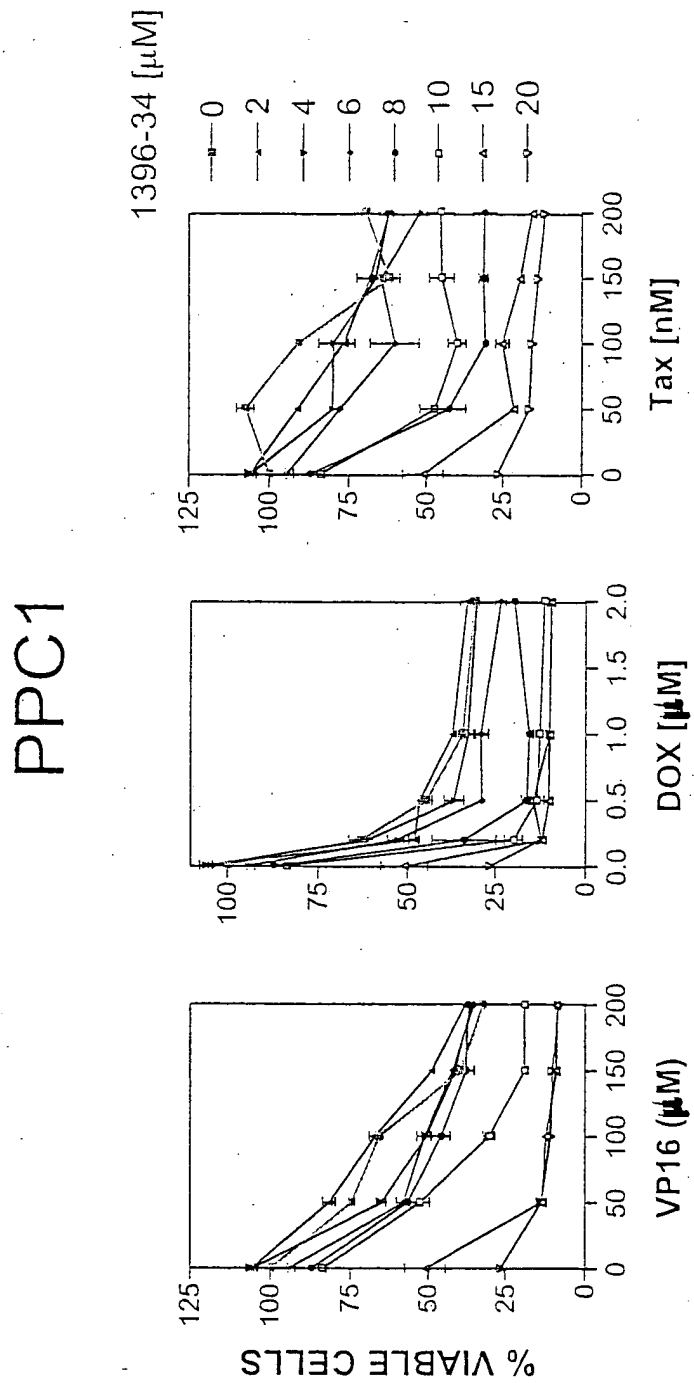

PPC1
% VIABLE CELLS
1396-34 [μM]
0
2
4
6
8
10
15
20
Tax [nM]
DOX [μM]
VP16 (μM)

FIGURE 31B

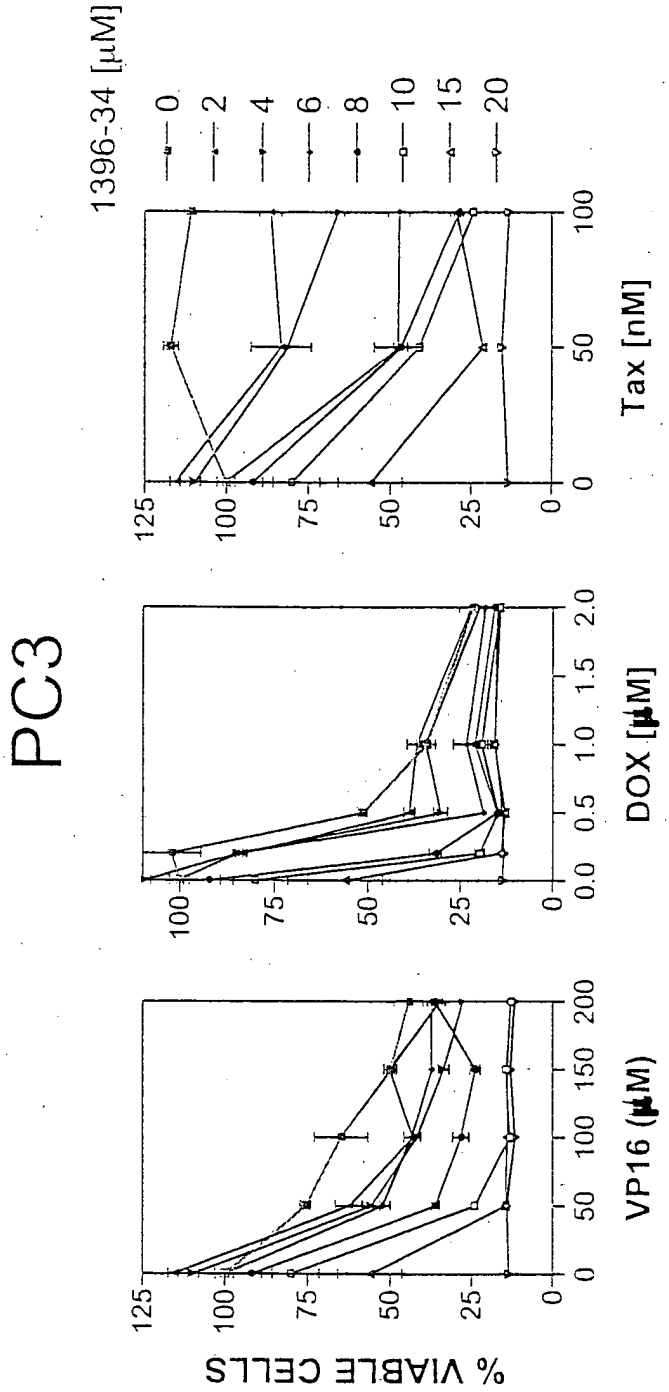


FIGURE 31C

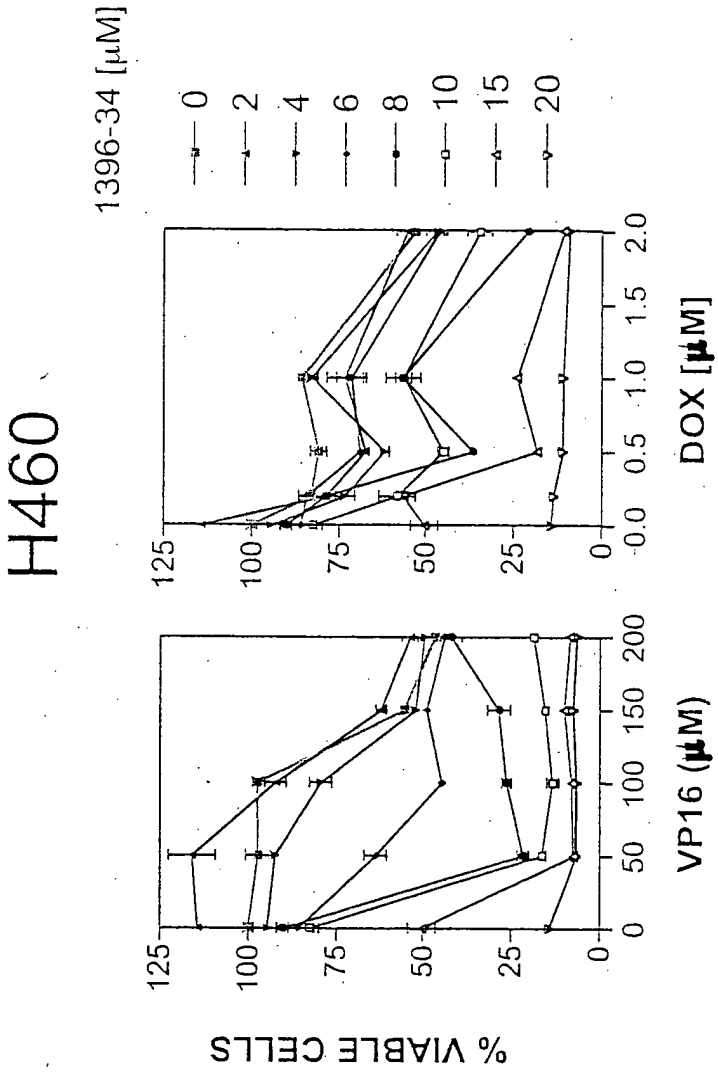

H460
1396-34 [μM]
0
2
4
6
8
10
15
20
% VIABLE CELLS
125
100
75
50
25
0
0.0
0.5
1.0
1.5
2.0
DOX [μM]
0
50
100
150
200
VP16 (μM)

FIGURE 31D

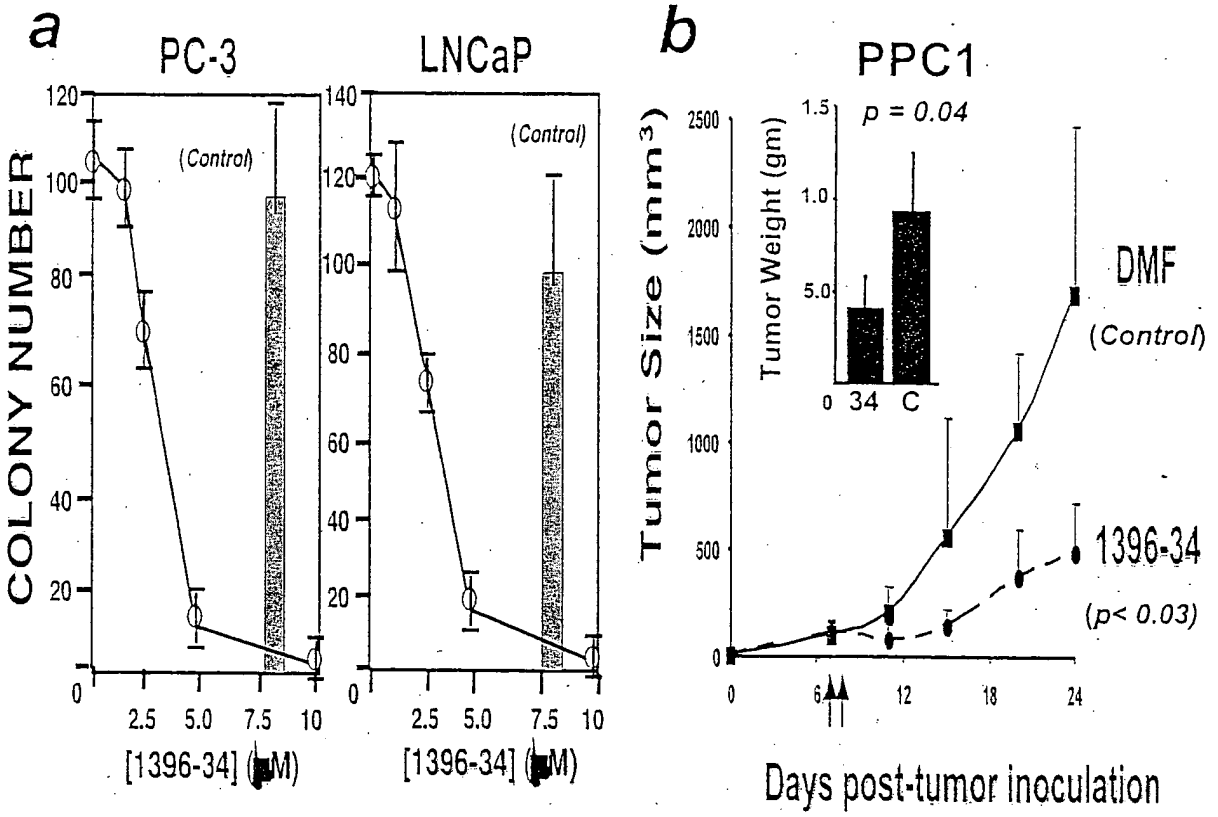

a
PC-3
LNCaP
COLONY NUMBER
(Control)
(Control)
[1396-34] (μM)
[1396-34] (μM)
b
PPC1
Tumor Size (mm³)
Tumor Weight (gm)
p = 0.04
DMF
(Control)
1396-34
(p< 0.03)
Days post-tumor inoculation
c
HCT116
Tumor Volume (cm³)
(p<0.001)
Tumor Weight (g)
(p<0.001)
I
C
I
C

FIGURE 32

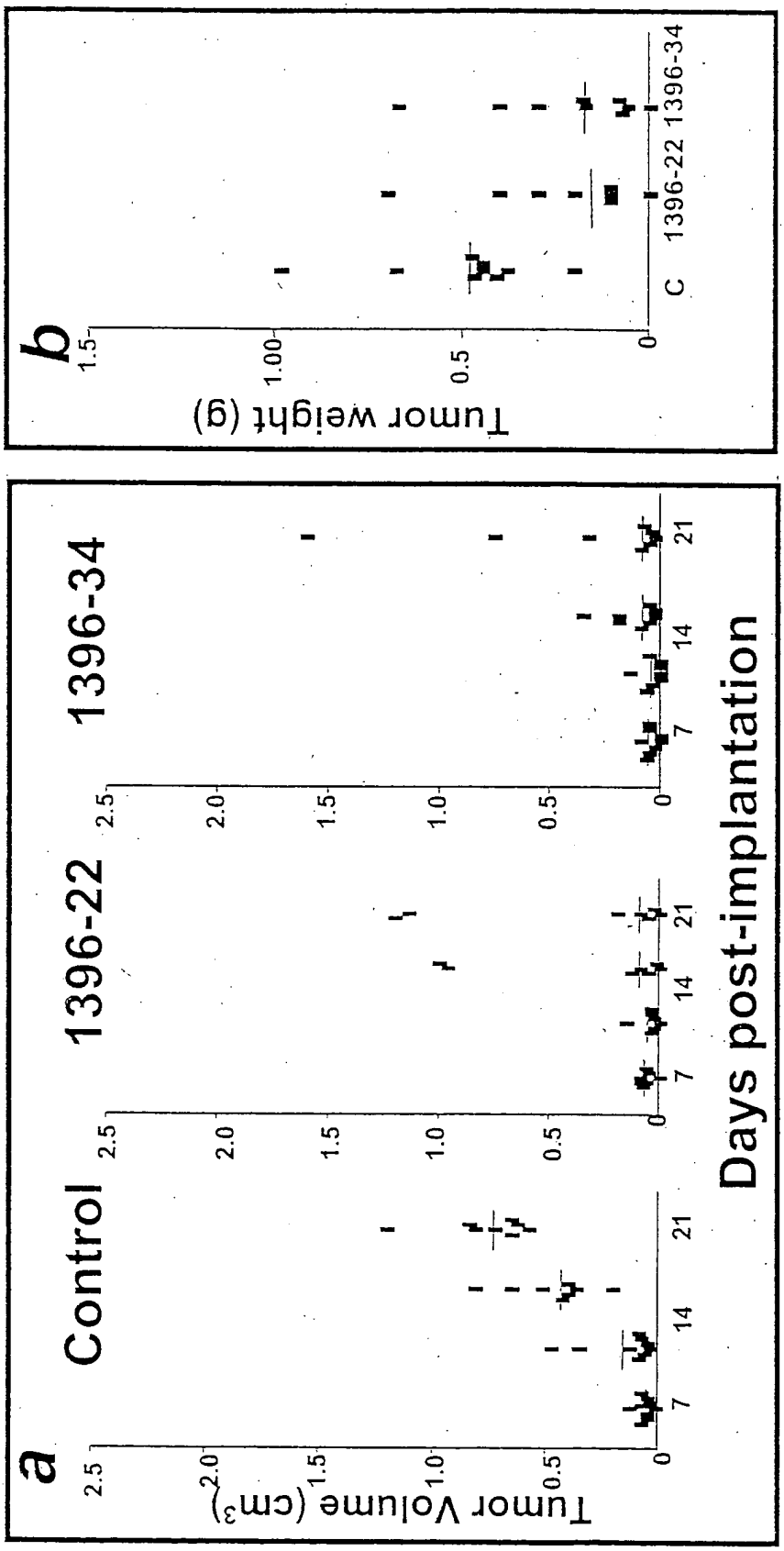

a
Control
1396-22
1396-34
Tumor Volume (cm3)
Days post-implantation
b
Tumor weight (g)
C
1396-22
1396-34

FIGURE 33

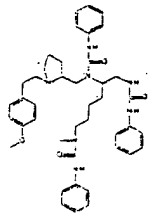
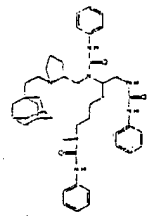
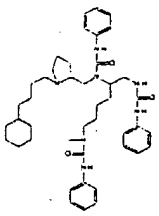
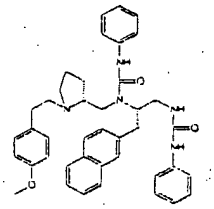
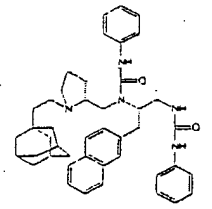
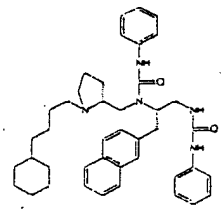
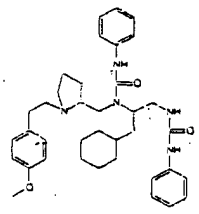
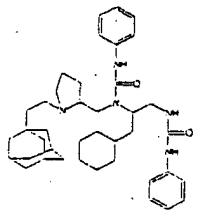
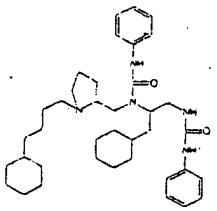
ID #	Name	MW	Structure	Relative caspase 3 activity @ 25 ug/ml	Relative caspase 3 activity lowest ug/ml
TPI 1509-1	N-[(5R)-6-[(anilinocarbonyl)amino]-5-[(anilinocarbonyl)[[(2R)-1-[2-(4-methoxyphenyl)ethyl]pyrrolidin-2-yl]methyl]amino]hexyl]-N-methyl-N'-phenylurea	719.9		2.0	6.25
TPI 1509-2	N-[[(2R)-1-[2-(1-adamantyl)ethyl]pyrrolidin-2-yl]methyl]-N-[(1R)-1-[[(anilinocarbonyl)amino]methyl]-5-[(anilinocarbonyl)(methyl)amino]pentyl]-N'-phenylurea	748.0		2.5	12.5
TPI 1509-3	N-[(5R)-6-[(anilinocarbonyl)amino]-5-[(anilinocarbonyl)[[(2R)-1-[4-cyclohexylbutyl]pyrrolidin-2-yl]methyl]amino]hexyl]-N-methyl-N'-phenylurea	724.0		2.4	12.5
TPI 1509-4	N-[(1S)-2-[(anilinocarbonyl)amino]-1-(2-naphthylmethyl)ethyl]-N-[[(2R)-1-[2-(4-methoxyphenyl)ethyl]pyrrolidin-2-yl]methyl]-N'-phenylurea	655.8		2.4	25
TPI 1509-5	N-[[(2R)-1-[2-(1-adamantyl)ethyl]pyrrolidin-2-yl]methyl]-N-[(1S)-2-[(anilinocarbonyl)amino]-1-(2-naphthylmethyl)ethyl]-N'-phenylurea	683.9		2.5	25
TPI 1509-6	N-[(1S)-2-[(anilinocarbonyl)amino]-1-(2-naphthylmethyl)ethyl]-N-[[(2R)-1-(4-cyclohexylbutyl)pyrrolidin-2-yl]methyl]-N'-phenylurea	659.9		2.0	12.5
TPI 1509-7	N-[(1R)-2-[(anilinocarbonyl)amino]-1-(cyclohexylmethyl)ethyl]-N-[[(2R)-1-[2-(4-methoxyphenyl)ethyl]pyrrolidin-2-yl]methyl]-N'-phenylurea	611.8		2.4	25

FIGURE 34

ID #	Name	MW	Structure	@ 25 ug/ml	(lowest ug/ml **
TPI 1509-8	N-{[(2R)-1-[2-(1-adamantyl)ethyl]pyrrolidin-2-yl]methyl}-N-[(1R)-2-[(anilinocarbonyl)amino]-1-(cyclohexylmethyl)ethyl]-N'-phenylurea	639.9		2.2	25
TPI 1509-9	N-[(1R)-2-[(anilinocarbonyl)amino]-1-(cyclohexylmethyl)ethyl]-N-{[(2R)-1-(4-cyclohexylbutyl)pyrrolidin-2-yl]methyl}-N'-phenylurea	615.9		2.2	25

Relative caspase-3* activity in the XIAP derepression assay was calculated as the ratio of the Vmax in the presence of each compound divided by the Vmax of the controls having caspase-3 and XIAP.
(lowest) ug/ml **: lowest concentration in which the relative caspase 3 activity was 1.8

FIGURE 34 (cont.)

TPI1509-7 Parent compound
D-Cyclohexylalanine, D-Proline

4.26 | 3 | 8 | 2

Lipinski Alerts: MW>500, MlogP > 4.15, HBD>5, HBA>10

FIGURE 35 TPI 1540
Code: 1077
Modifications of TPI1509-7

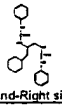
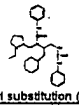
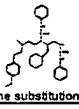
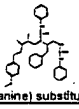
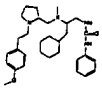
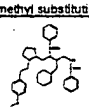
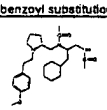
	Structure	MW	Modification	R group	Yield (mg)	MLogP	Hydrogen Bond Donors	Hydrogen Bond Acceptors	Lipinski Alerts
6	 L-cyclohexylalanine analog	611.38	Sterochemistry	R1	54.3	4.26	3	8	2
7	 L-Proline,L-cyclohexylalanine analog	611.38	Sterochemistry	R1 and R2	64.4	4.26	3	8	2
8	 Split parent compound-Left side	353.21	Removal of R1 and associated urea	R1	14.8	2.63	2	5	0
9	 Split parent compound-Right side	394.24	Removal of R2 and R3	R2 and R3	32	3.02	4	6	0
10	 Remove R3	477.31	Removal of R3	R3	5.6	3.29	4	7	0
11	 Remove R3-Acetyl substitution (ethyl)	505.3	Replacement of R3 with ethyl	R3	51.1	3.68	3	7	1
12	 Remove R2-Glycine substitution	585.37	Removal of R2	R2	56.1	3.90	3	8	1
13	 Remove R2-(O-Alanine) substitution	599.38	Replacement of pyrrolidine with N-metylalanine	R2	60.2	4.08	3	8	1
14	 Remove urea 2-methyl substitution	506.36	Removal of N-urea	Urea	48.7	3.89	2	6	1
15	 Remove R1-Glycine substitution	515.2	Removal of R1	R1	51.2	2.97	3	8	1
16	 Remove R1-(O-Alanine) substitution	529.31	Replacement of R1 with methyl	R1	51.5	3.16	3	8	1
17	 Remove urea 1-methyl substitution	506.36	Removal of N'-urea	Urea	10.3	3.89	2	6	1
18	 Remove ureas-benzoyl substitution	581.36	Replacement of phenylurea with phenylacyl	Urea	15.2	4.95	1	6	2
19	 Remove ureas-acetylate	457.33	Replacement of phenylurea with acetyl	Urea	18.8	3.01	1	6	0

FIGURE 35A

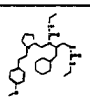
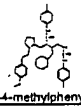
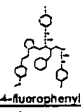
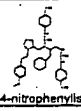
20	 Urea substitution-ethyl isocyanate	515.38	Replacement of phenylurea with ethylurea	Urea	53	2.71	3	8	1
21	 Urea substitution-4-methylphenylisocyanate	639.41	Replacement of phenylurea with p-methylphenylurea	Urea	67.7	4.61	3	8	2
22	 Urea substitution-4-fluorophenylisocyanate	647.36	Replacement of phenylurea with p-fluorophenylurea	Urea	72.2	4.70	3	8	2
23	 Urea substitution-4-nitrophenylisocyanate	701.35	Replacement of phenylurea with p-nitrophenylurea	Urea	66.4	4.39	3	14	3

FIGURE 35A (cont.)

SAR of active poly-phenylurea (TPI 1509-7)

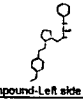
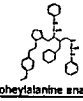
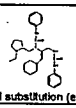
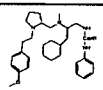
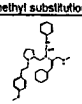
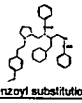
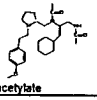
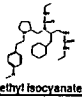
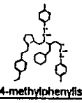
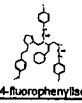
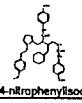
TPI 1540-	Structure	MW	Modification	R group	Caspase 3-XIAP derepression* Ratio** 100 ug/ml	25 ug/ml	IC-50 uM	Summ activity	TPIMS IC-50-MTT uM *** Jurkatt	MCF-7	Annexin-V Jurkatt IC-50 uM
TPI 1509-7		611.82	Native-R2=D-proline		2.4	1.7	36.0	++	10.8	>163	5.2
TPI 1507 21-30 (TPI 1396-34)		611.82	R2=L-Proline		2.2	1.6	57.2	++	14.7	>163	N.T
6	 L-cyclohexylalanine analog	611.38	Sterochemistry	R1	2.2	1.8	39.3	++	9.8	74.7	N.T
15	 Remove R1-Glycine substitution	515.2	Removal of R1	R1	2	1.4	97.0	++	11.5	15.5	6.3
16	 Remove R1-(D-Alanine) substitution	529.31	Replacement of R1 with methyl	R1	2	1.3	102.0	++	15.4	18.4	>30
8	 Split parent compound-Left side	353.21	Removal of R1 and associated urea	R1	1.2	0.9	>283	_	247.0	259.3	N.T
7	 L-Proline,L-cycloheytalanine analog	611.38	Sterochemistry	R1 and R2	2.3	1.7	40.9	++	53.5	155.1	N.T
12	 Remove R2-Glycine substitution	585.37	Removal of R2	R2	2.2	1.6	54.7	++	43.9	>171	7.1
13	 Remove R2-(D-Alanine) substitution	599.38	Replacement of pyrrolidine with N-metylalanine	R2	2.3	1.7	45.0	++	15.8	>167	4.9
9	 Split parent compound-Right side	394.24	Removal of R2 and R3	R2 and R3	1.1	0.9	>254	_	>254	142.3	N.T

FIGURE 35B

					Ratio**				IC-50-MTT uM ***		Jurkatt
TPI 1540-	Structure	MW	Modification	R group	100 ug/ml	25 ug/ml	IC-50 uM	Summ activity	Jurkatt	MCF-7	IC-50 uM
10	 Remove R3	477.31	Removal of R3	R3	1.5	0.9	>210	-	128.8	150.0	N.T
11	 Remove R3-Acetyl substitution (ethyl)	505.3	Replacement of R3 with ethyl	R3	2.2	1.7	49.5	++	16.0	25.7	7.6
14	 Remove urea 2-methyl substitution	506.36	Removal of N-urea	Urea	2	1.8	43.4	++	19.2	21.4	7.3
17	 Remove urea 1-methyl substitution	506.36	Removal of N'-urea	Urea	1.7	1.4	175.8	+	16.0	10.0	N.T
18	 Remove ureas-benzoyl substitution	581.36	Replacement of phenylurea with phenylacyl	Urea	1.8	1.2	154.8	+	38.9	24.5	N.T
19	 Remove ureas-acetylate	457.33	Replacement of phenylurea with acetyl	Urea	1.2	0.9	218.7	-	127.9	87.4	N.T
20	 Urea substitution-ethyl isocyanate	515.38	Replacement of phenylurea with ethylurea	Urea	1.6	1	194.0	-	92.8	>194	>30
21	 Urea substitution-4-methylphenylisocyanate	639.41	Replacement of phenylurea with p-methylphenylurea	Urea	2.3	1.7	42.2	++	32.1	>156	5.4
22	 Urea substitution-4-fluorophenylisocyanate	647.36	Replacement of phenylurea with p-fluorophenylurea	Urea	1.1	1.5	55.6	++	14.5	102.0	3.9
23	 Urea substitution-4-nitrophenylisocyanate	701.35	Replacement of phenylurea with p-nitrophenylurea	Urea	1.6	1.2	>143	+	74.0	117.2	N.T

Caspase-XIAP derepression assay*:crude compounds/080603
Ratio** =Vmax compound+C3+XIAP/Vmax C3+XIAP
++: As active as native or not more than 20 % decrease
+: less active, ~30 % reduction
-:No activity at 100 ug/ml
MTT data***=activity for crude and pur compounds, pure ones are:11,12,13,14,15,16,20,21,22
11,12,13,14,15,16,20,21,22

FIGURE 35B (cont.)

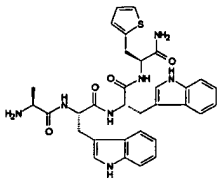
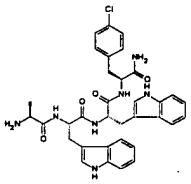
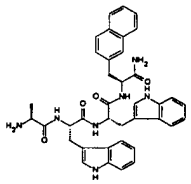
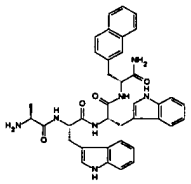
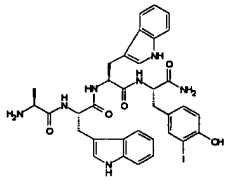
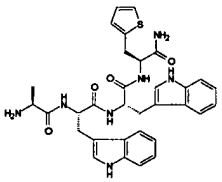
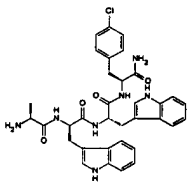
TPI1332	Structure	MW
1	 [L-Ala][L-Trp(CHO)][L-Trp(CHO)][L-ThiAla]	613.74
2	 [L-Ala][L-Trp(CHO)][L-Trp(CHO)][L-pClPhe]	642.16
3	 [L-Ala][L-Trp(CHO)][L-Trp(CHO)][L-Nal]	657.77
4	 [L-Ala][L-Trp(CHO)][L-Trp(CHO)][D-Nal]	657.77
5	 [L-Ala][L-Trp(CHO)][L-Trp(CHO)][L-3I-Tyr]	749.61
6	 [L-Ala][D-Trp(CHO)][L-Trp(CHO)][L-ThiAla]	613.74
7	 [L-Ala][D-Trp(CHO)][L-Trp(CHO)][L-pClPhe]	642.16

FIGURE 36A

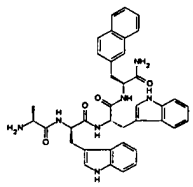
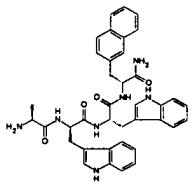
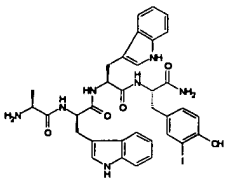
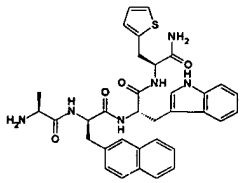
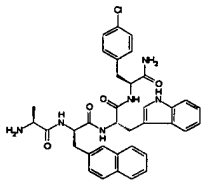
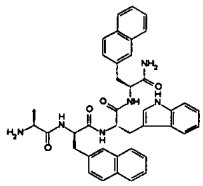
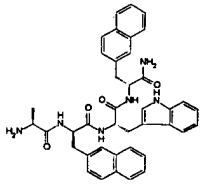
TPI1332	Structure	MW
8	 [L-Ala][D-Trp(CHO)][L-Trp(CHO)][L-Nal]	657.77
9	 [L-Ala][D-Trp(CHO)][L-Trp(CHO)][D-Nal]	657.77
10	 [L-Ala][D-Trp(CHO)][L-Trp(CHO)][L-3I-Tyr]	749.61
11	 [L-Ala][D-Nal][L-Trp(CHO)][L-ThiAla]	624.76
12	 [L-Ala][D-Nal][L-Trp(CHO)][L-pClPhe]	653.18
13	 [L-Ala][D-Nal][L-Trp(CHO)][L-Nal]	668.80
14	 [L-Ala][D-Nal][L-Trp(CHO)][D-Nal]	668.80

FIGURE 36A (cont.)

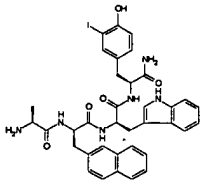
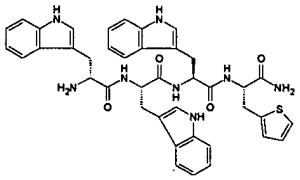
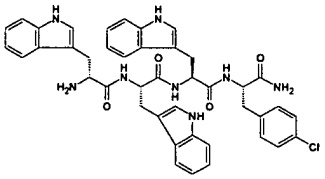
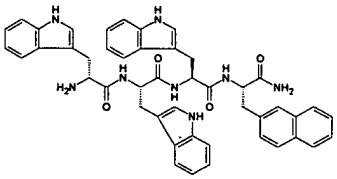
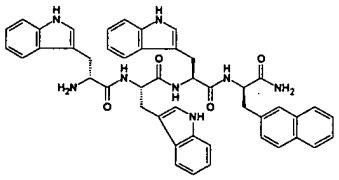
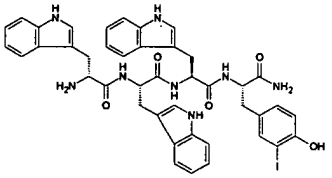
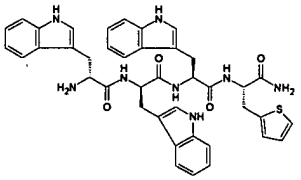
TPI1332	Structure	MW
15	 [L-Ala][D-Nal][L-Trp(CHO)][L-3I-Tyr]	760.63
16	 [D-Trp(CHO)][L-Trp(CHO)][L-Trp(CHO)][L-ThiAla]	728.88
17	 [D-Trp(CHO)][L-Trp(CHO)][L-Trp(CHO)][L-pClPhe]	757.29
18	 [D-Trp(CHO)][L-Trp(CHO)][L-Trp(CHO)][L-Nal]	772.91
19	 [D-Trp(CHO)][L-Trp(CHO)][L-Trp(CHO)][D-Nal]	772.91
20	 [D-Trp(CHO)][L-Trp(CHO)][L-Trp(CHO)][L-3I-Tyr]	864.74
21	 [D-Trp(CHO)][D-Trp(CHO)][L-Trp(CHO)][L-ThiAla]	728.88

FIGURE 36A (cont.)

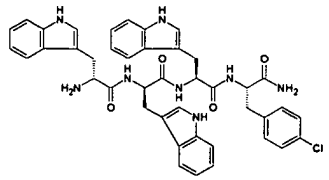
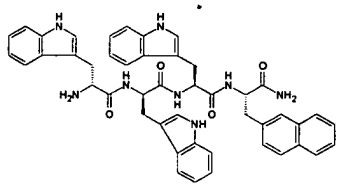
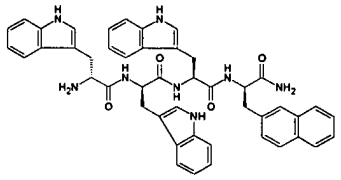
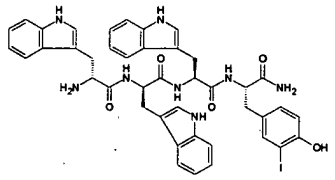
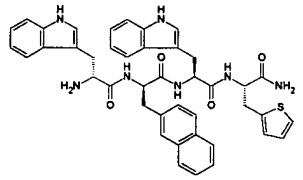
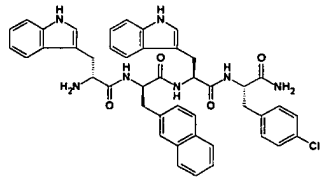
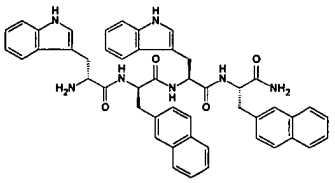
TPI1332	Structure	MW
22	 [D-Trp(CHO)][D-Trp(CHO)][L-Trp(CHO)][L-pClPhe]	757.29
23	 [D-Trp(CHO)][D-Trp(CHO)][L-Trp(CHO)][L-Nal]	772.91
24	 [D-Trp(CHO)][D-Trp(CHO)][L-Trp(CHO)][D-Nal]	772.91
25	 [D-Trp(CHO)][D-Trp(CHO)][L-Trp(CHO)][L-3I-Tyr]	864.74
26	 [D-Trp(CHO)][D-Nal][L-Trp(CHO)][L-ThiAla]	739.90
27	 [D-Trp(CHO)][D-Nal][L-Trp(CHO)][L-pClPhe]	768.32
28	 [D-Trp(CHO)][D-Nal][L-Trp(CHO)][L-Nal]	783.93

FIGURE 36A (cont.)

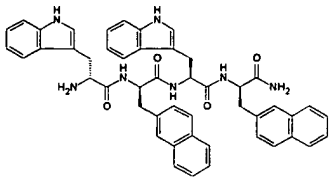
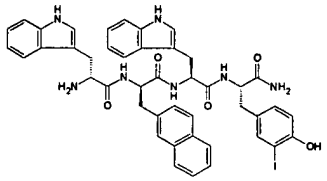
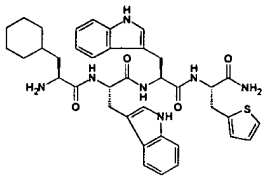
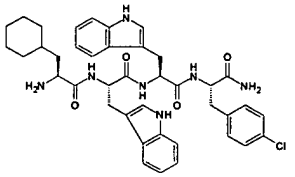
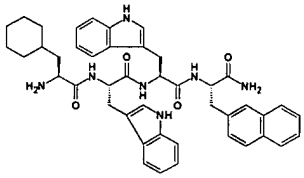
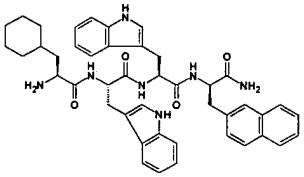
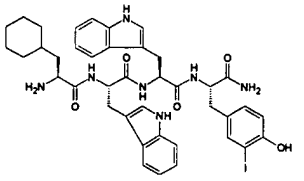
TPI1332	Structure	MW
29	 [D-Trp(CHO)][D-Nal][L-Trp(CHO)][D-Nal]	783.93
30	 [D-Trp(CHO)][D-Nal][L-Trp(CHO)][L-3I-Tyr]	875.77
31	 [L-Cha][L-Trp(CHO)][L-Trp(CHO)][L-ThiAla]	695.89
32	 [L-Cha][L-Trp(CHO)][L-Trp(CHO)][L-pClPhe]	724.31
33	 [L-Cha][L-Trp(CHO)][L-Trp(CHO)][L-Nal]	739.92
34	 [L-Cha][L-Trp(CHO)][L-Trp(CHO)][D-Nal]	739.92
35	 [L-Cha][L-Trp(CHO)][L-Trp(CHO)][L-3I-Tyr]	831.76

FIGURE 36A (cont.)

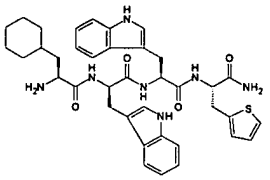
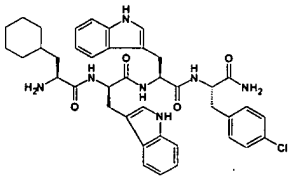
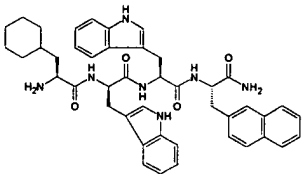
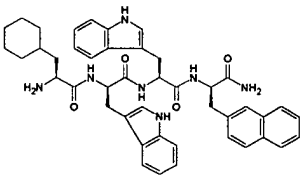
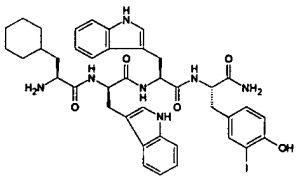
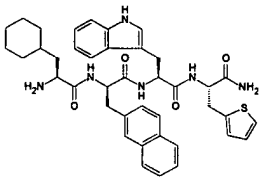
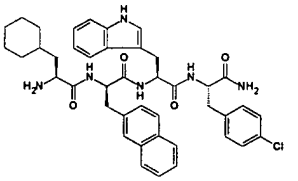
TPI1332	Structure	MW
36	 [L-Cha][D-Trp(CHO)][L-Trp(CHO)][L-ThiAla]	695.89
37	 [L-Cha][D-Trp(CHO)][L-Trp(CHO)][L-pClPhe]	724.31
38	 [L-Cha][D-Trp(CHO)][L-Trp(CHO)][L-Nal]	739.92
39	 [L-Cha][D-Trp(CHO)][L-Trp(CHO)][D-Nal]	739.92
40	 [L-Cha][D-Trp(CHO)][L-Trp(CHO)][L-3I-Tyr]	831.76
41	 [L-Cha][D-Nal][L-Trp(CHO)][L-ThiAla]	706.91
42	 [L-Cha][D-Nal][L-Trp(CHO)][L-pClPhe]	735.33

FIGURE 36A (cont.)

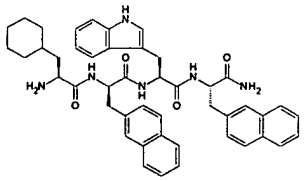
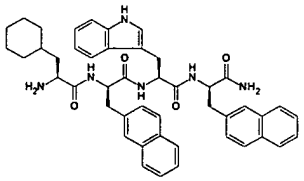
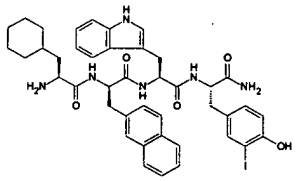
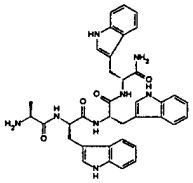
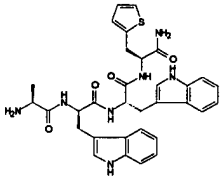
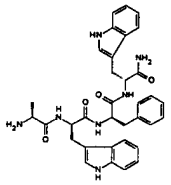
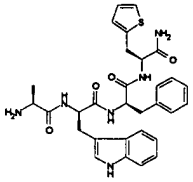
TPI1332	Structure	MW
43	 [L-Cha][D-Nal][L-Trp(CHO)][L-Nal]	750.94
44	 [L-Cha][D-Nal][L-Trp(CHO)][D-Nal]	750.94
45	 [L-Cha][D-Nal][L-Trp(CHO)][L-3I-Tyr]	842.78
46	 [L-Ala][D-Trp(CHO)][L-Trp(CHO)][D-Trp(CHO)]	646.75
47	 [L-Ala][D-Trp(CHO)][L-Trp(CHO)][L-ThiAla]	613.74
48	 [L-Ala][D-Trp(CHO)][D-Phe][D-Trp(CHO)]	607.71
49	 [L-Ala][D-Trp(CHO)][D-Phe][L-ThiAla]	574.70

FIGURE 36A (cont.)

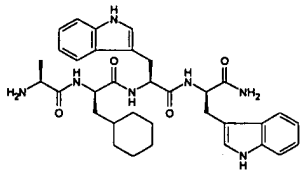
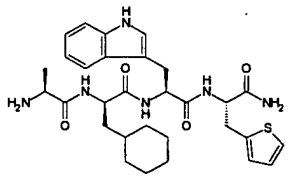
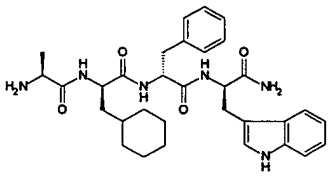
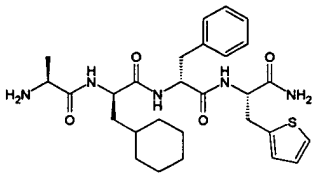
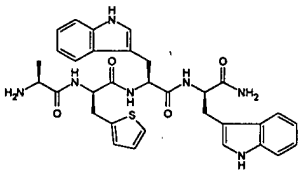
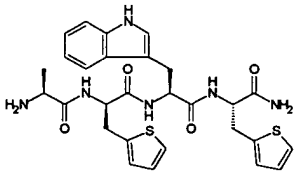
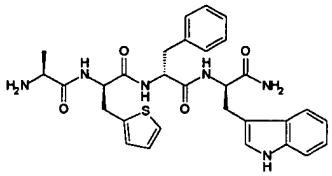
TPI1332	Structure	MW
50	 [L-Ala][D-Cha][L-Trp(CHO)][D-Trp(CHO)]	613.76
51	 [L-Ala][D-Cha][L-Trp(CHO)][L-ThiAla]	580.75
52	 [L-Ala][D-Cha][D-Phe][D-Trp(CHO)]	574.73
53	 [L-Ala][D-Cha][D-Phe][L-ThiAla]	541.71
54	 [L-Ala][D-ThiAla][L-Trp(CHO)][D-Trp(CHO)]	613.74
55	 [L-Ala][D-ThiAla][L-Trp(CHO)][L-ThiAla]	580.73
56	 [L-Ala][D-ThiAla][D-Phe][D-Trp(CHO)]	574.70

FIGURE 36A (cont.)

TPI1332	Structure	MW
57	[L-Ala][D-ThiAla][D-Phe][L-ThiAla]	541.69
58	[L-Ala][D-pIPhe][L-Trp(CHO)][D-Trp(CHO)]	733.61
59	[L-Ala][D-pIPhe][L-Trp(CHO)][L-ThiAla]	700.60
60	[L-Ala][D-pIPhe][D-Phe][D-Trp(CHO)]	694.57
61	[L-Ala][D-pIPhe][D-Phe][L-ThiAla]	661.56
62	[L-Nal][D-Trp(CHO)][L-Trp(CHO)][D-Trp(CHO)]	772.91
63	[L-Nal][D-Trp(CHO)][L-Trp(CHO)][L-ThiAla]	739.90

FIGURE 36A (cont.)

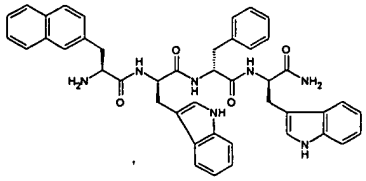
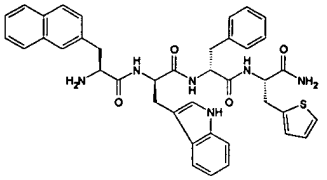
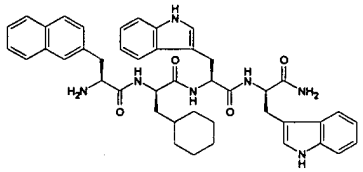
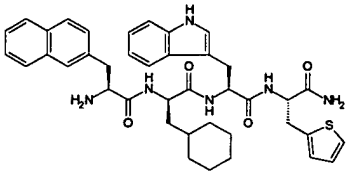
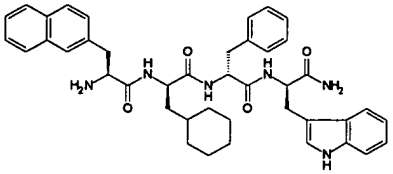
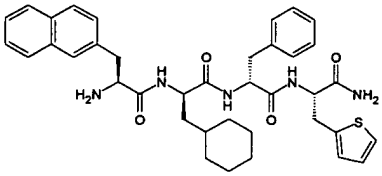
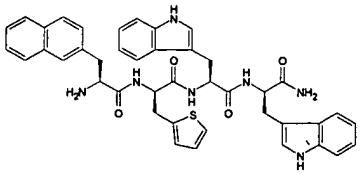
TPI1332	Structure	MW
64	 [L-Nal][D-Trp(CHO)][D-Phe][D-Trp(CHO)]	733.87
65	 [L-Nal][D-Trp(CHO)][D-Phe][L-ThiAla]	700.86
66	 [L-Nal][D-Cha][L-Trp(CHO)][D-Trp(CHO)]	739.92
67	 [L-Nal][D-Cha][L-Trp(CHO)][L-ThiAla]	706.91
68	 [L-Nal][D-Cha][D-Phe][D-Trp(CHO)]	700.88
69	 [L-Nal][D-Cha][D-Phe][L-ThiAla]	667.87
70	 [L-Nal][D-ThiAla][L-Trp(CHO)][D-Trp(CHO)]	739.90

FIGURE 36A (cont.)

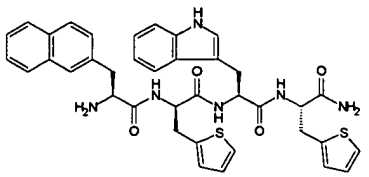
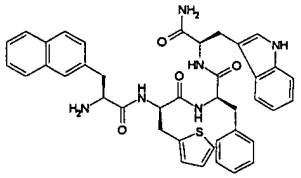
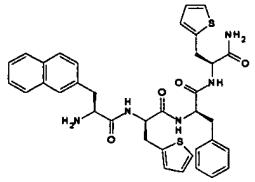
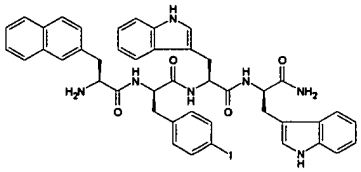
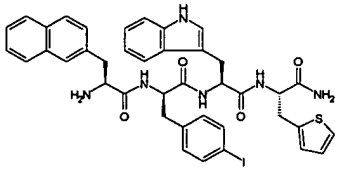
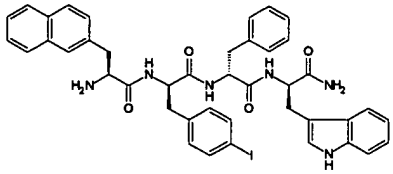
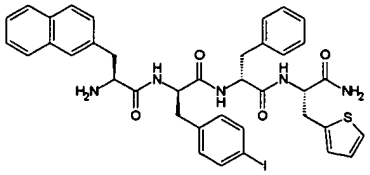
TPI1332	Structure	MW
71	 [L-Nal][D-ThiAla][L-Trp(CHO)][L-ThiAla]	706.89
72	 [L-Nal][D-ThiAla][D-Phe][D-Trp(CHO)]	700.86
73	 [L-Nal][D-ThiAla][D-Phe][L-ThiAla]	667.85
74	 [L-Nal][D-pIPhe][L-Trp(CHO)][D-Trp(CHO)]	859.77
75	 [L-Nal][D-pIPhe][L-Trp(CHO)][L-ThiAla]	826.76
76	 [L-Nal][D-pIPhe][D-Phe][D-Trp(CHO)]	820.73
77	 [L-Nal][D-pIPhe][D-Phe][L-ThiAla]	787.72

FIGURE 36A (cont.)

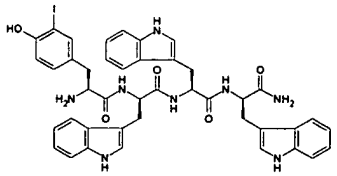
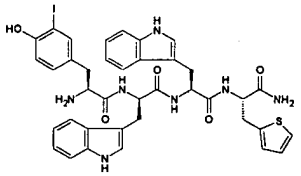
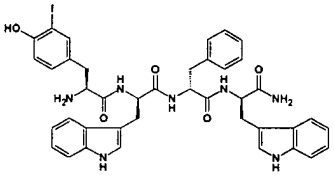
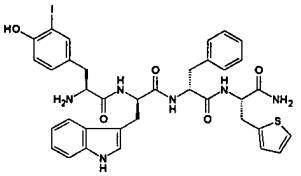
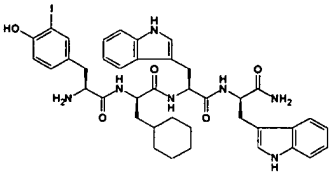
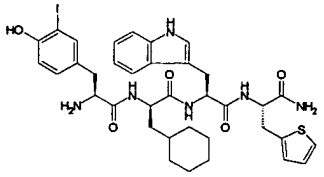
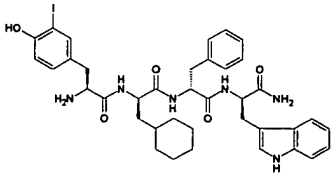
TPI1332	Structure	MW
78	 [L-3I-Tyr][D-Trp(CHO)][L-Trp(CHO)][D-Trp(CHO)]	864.74
79	 [L-3I-Tyr][D-Trp(CHO)][L-Trp(CHO)][L-ThiAla]	831.73
80	 [L-3I-Tyr][D-Trp(CHO)][D-Phe][D-Trp(CHO)]	825.71
81	 [L-3I-Tyr][D-Trp(CHO)][D-Phe][L-ThiAla]	792.70
82	 [L-3I-Tyr][D-Cha][L-Trp(CHO)][D-Trp(CHO)]	831.76
83	 [L-3I-Tyr][D-Cha][L-Trp(CHO)][L-ThiAla]	798.74
84	 [L-3I-Tyr][D-Cha][D-Phe][D-Trp(CHO)]	792.72

FIGURE 36A (cont.)

TPI1332	Structure	MW
85	[L-3I-Tyr][D-Cha][D-Phe][L-ThiAla]	759.71
86	[L-3I-Tyr][D-ThiAla][L-Trp(CHO)][D-Trp(CHO)]	831.73
87	[L-3I-Tyr][D-ThiAla][L-Trp(CHO)][L-ThiAla]	798.72
88	[L-3I-Tyr][D-ThiAla][D-Phe][D-Trp(CHO)]	792.70
89	[L-3I-Tyr][D-ThiAla][D-Phe][L-ThiAla]	759.69
90	[L-3I-Tyr][D-pIPhe][L-Trp(CHO)][D-Trp(CHO)]	951.60
91	[L-3I-Tyr][D-pIPhe][L-Trp(CHO)][L-ThiAla]	918.59

FIGURE 36A (cont.)

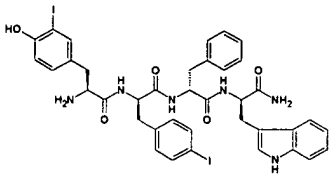
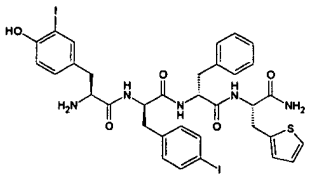
TPI1332	Structure	MW
92	 [L-3I-Tyr][D-pIPhe][D-Phe][D-Trp(CHO)]	912.57
93	 [L-3I-Tyr][D-pIPhe][D-Phe][L-ThiAla]	879.56

FIGURE 36A (cont.)

XIAP inhibitors-Tetrapeptides

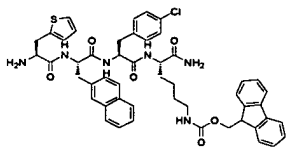
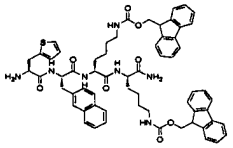
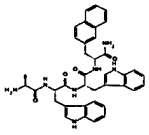
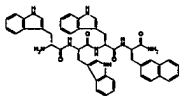
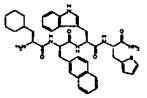
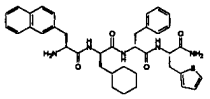
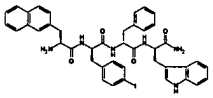
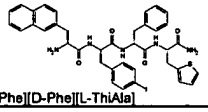
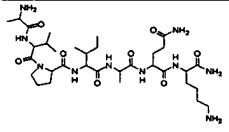
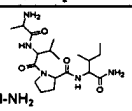
		MW	Competition assay Smac-7 mer/XIAP-BIR2 IC-50 uM AVG	STD
TPI 1453-1 (TPI 792-33)	 Exact Mass: 898.32793 [L-ThiAla]-[L-Nal]-[p-ClPhe]-[L-LyseFmoc]	900.9	48.4	10
TPI 1453-6 (TPI 792-35)	 [L-ThiAla]-[L-Nal]-[p-ClPhe]-[L-LyseFmoc]	1068.8	12.6	4.8
TPI1332-4	 [L-Ala][L-Trp(CHO)][L-Trp(CHO)][D-Nal]	657.8	3.9	3.6
TPI 1332-24	 [D-Trp(CHO)][D-Trp(CHO)][L-Trp(CHO)][D-Nal]	772.9	5.0	4.8
TPI1332-41	 [L-Cha][D-Nal][L-Trp(CHO)][L-ThiAla]	706.9	48.5	0.9
TPI 1332-69	 [L-Nal][D-Cha][D-Phe][L-ThiAla]	667.9	>150	
TPI 1332-76	 [L-Nal][D-pIPhe][D-Phe][D-Trp(CHO)]	820.7	36.2	20.9
TPI 1332-77	 [L-Nal][D-pIPhe][D-Phe][L-ThiAla]	787.7	66.7	32.4
Smac 7-mer	 AVPIAQK-NH_2	724.4	18.8	4
Smac 4-mer	 AVPI-NH_2	397.2	30.3	

FIGURE 36B

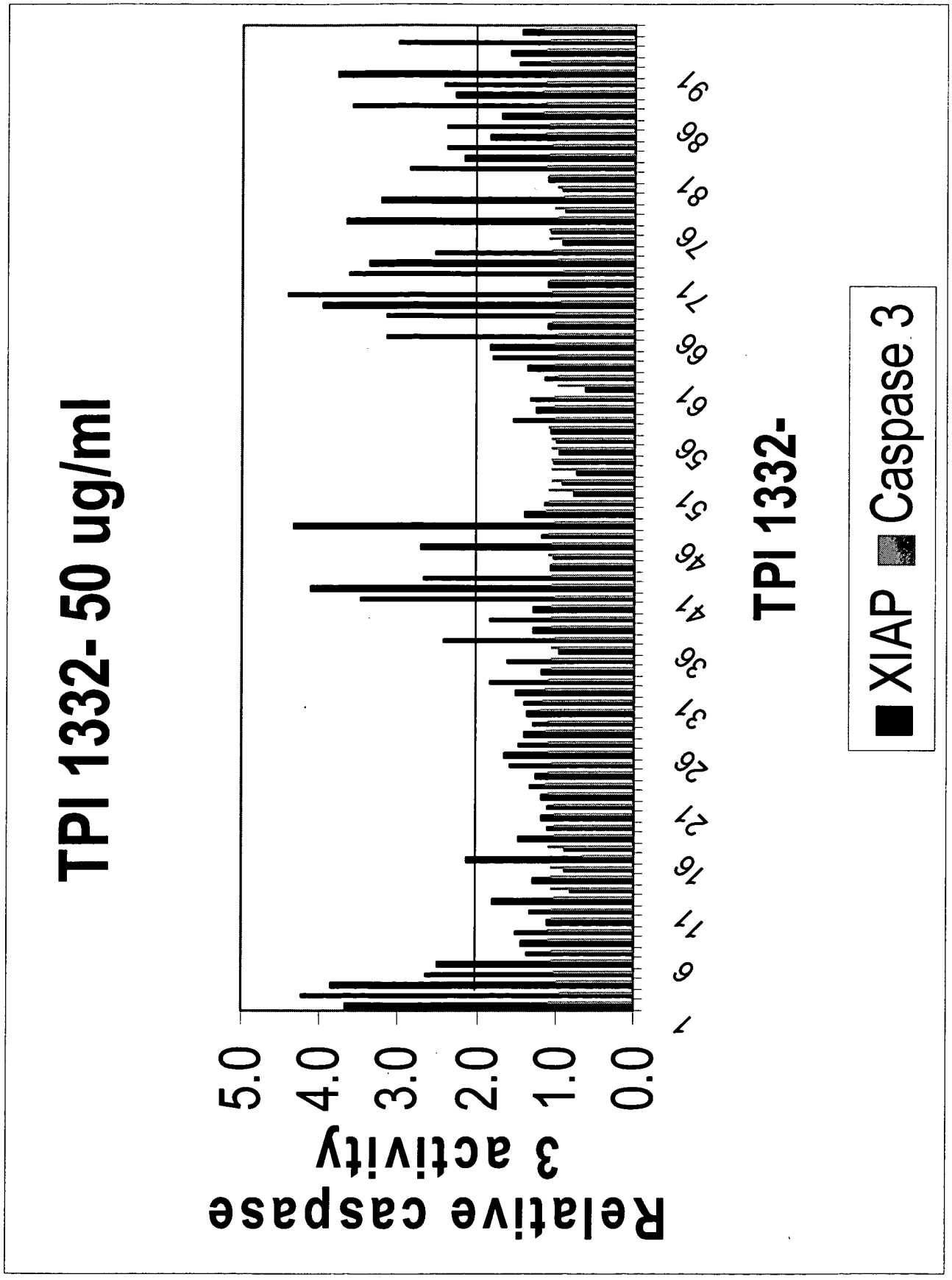

TPI 1332- 50 ug/ml
TPI 1332-
XIAP
Caspase 3
Relative caspase 3 activity
5.0
4.0
3.0
2.0
1.0
0.0
1
6
11
16
21
26
31
36
41
46
51
56
61
66
71
76
81
86
91

FIGURE 36C

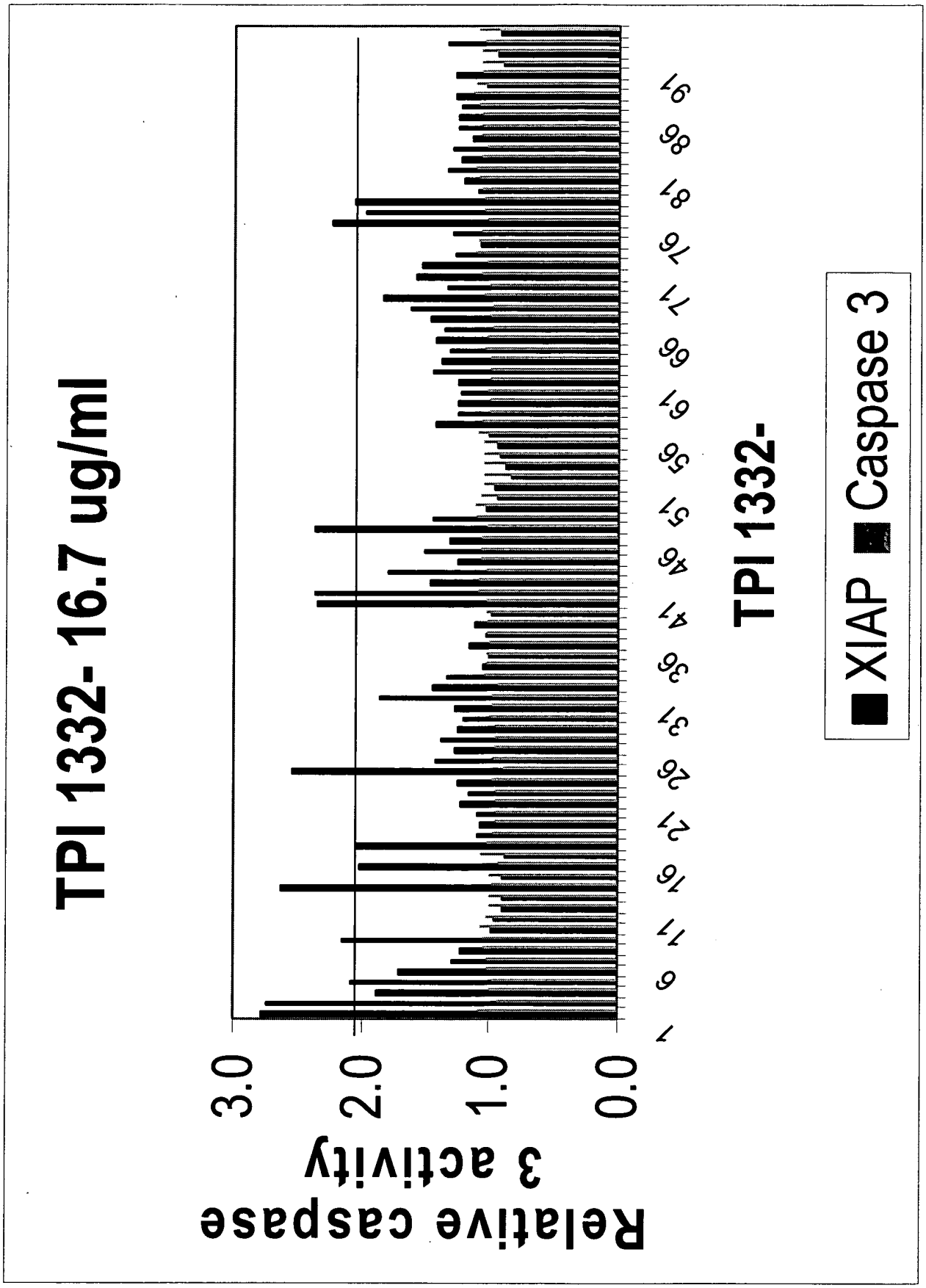

TPI 1332- 16.7 ug/ml
TPI 1332-
XIAP
Caspase 3
Relative caspase 3 activity
3.0
2.0
1.0
0.0
1
6
11
16
21
26
31
36
41
46
51
56
61
66
71
76
81
86
91

FIGURE 36D

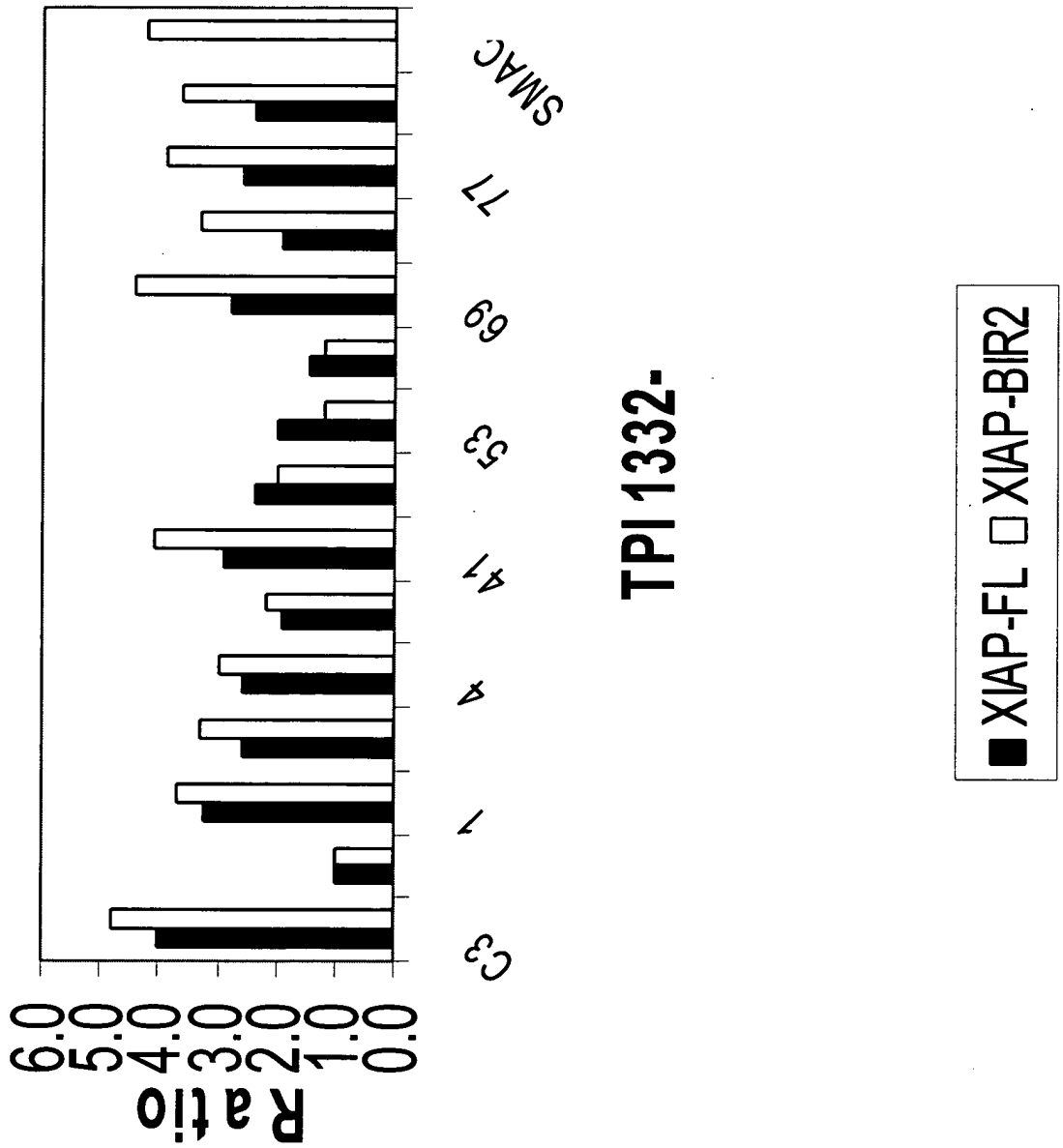

Ratio
6.0
5.0
4.0
3.0
2.0
1.0
0.0
C3
1
4
47
53
69
77
SMAC
TPI 1332-
XIAP-FL
XIAP-BIR2

FIGURE 36E

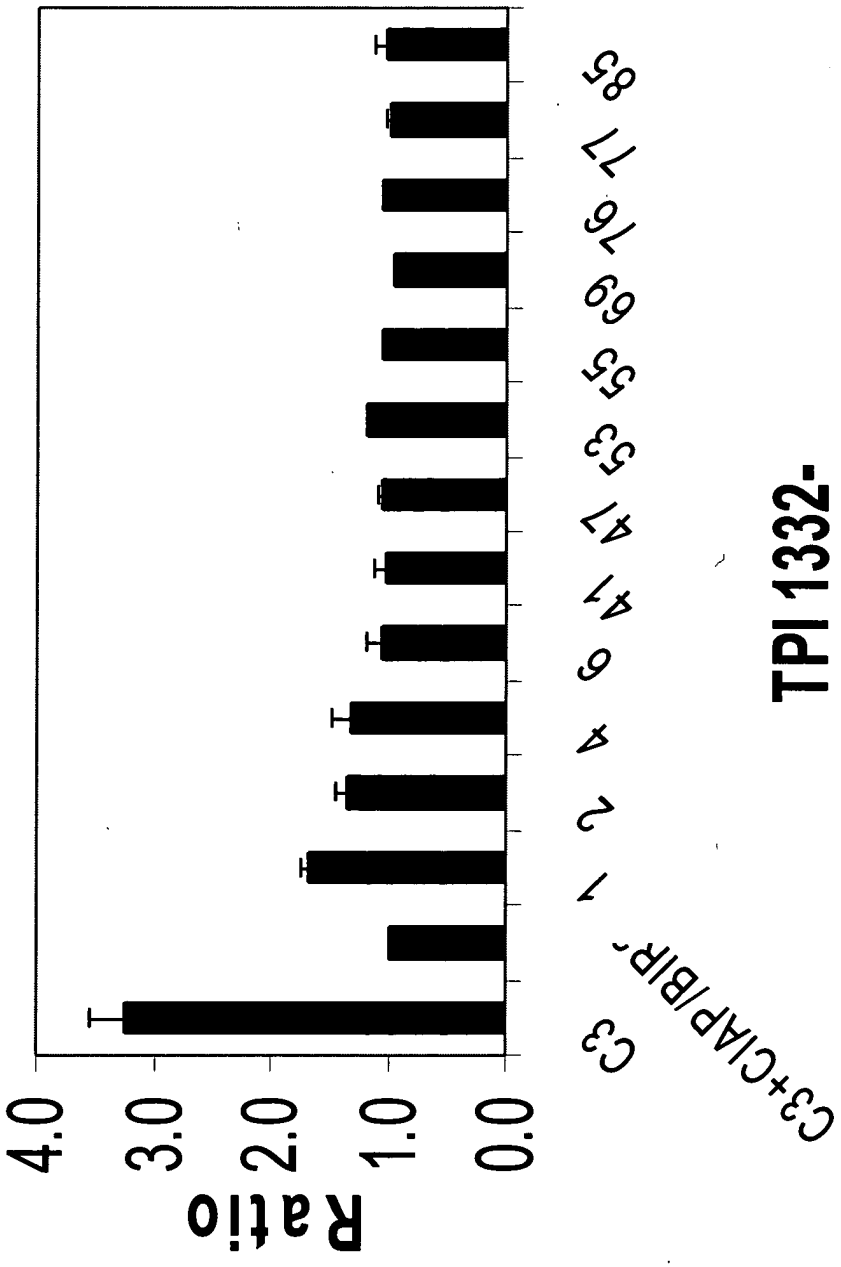

Ratio
4.0
3.0
2.0
1.0
0.0
C3
C3+CIAP/BIR-
1
2
4
6
47
47
53
55
69
76
77
85
TPI 1332-

FIGURE 36F

TPI 1495-1 is the same as TPI 1332-69

TPI 1495-							MW	XIAP-FL derepression IC50 uM	Competitive binding assay IC-50 uM	STD
1	H-	L-Nal	D-Cha	D-Phe	L-ThiaAla	-NH2	667.3	**33.9**	**>150**	
2	H-	**G**	D-Cha	D-Phe	L-ThiaAla	-NH2	527.3	**>189.7**	**>190**	
3	H-	L-Nal	**G**	D-Phe	L-ThiaAla	-NH2	571.2	**>175.1**	**>175**	
4	H-	L-Nal	D-Cha	**G**	L-ThiaAla	-NH2	577.3	**>173.2**	**>175**	
5	H-	L-Nal	D-Cha	D-Phe	**G**	-NH2	571.3	**67.4**	**29.7**	23.4
6	H-	**A**	D-Cha	D-Phe	L-ThiaAla	-NH2	541.3	**>184.8**	**>185**	
7	H-	L-Nal	**A**	D-Phe	L-ThiaAla	-NH2	585.2	**>170.9**	**>170**	
8	H-	L-Nal	D-Cha	**A**	L-ThiaAla	-NH2	591.3	**>169.1**	**>170**	
9	H-	L-Nal	D-Cha	D-Phe	**A**	-NH2	585.3	**149.0**	**>170**	

TPI 1237-	Smac 7 mer					724.4		**18.8**	4.0
TPI 1425-	Smac 4 mer					397.2		**30.3**	

FIGURE 37

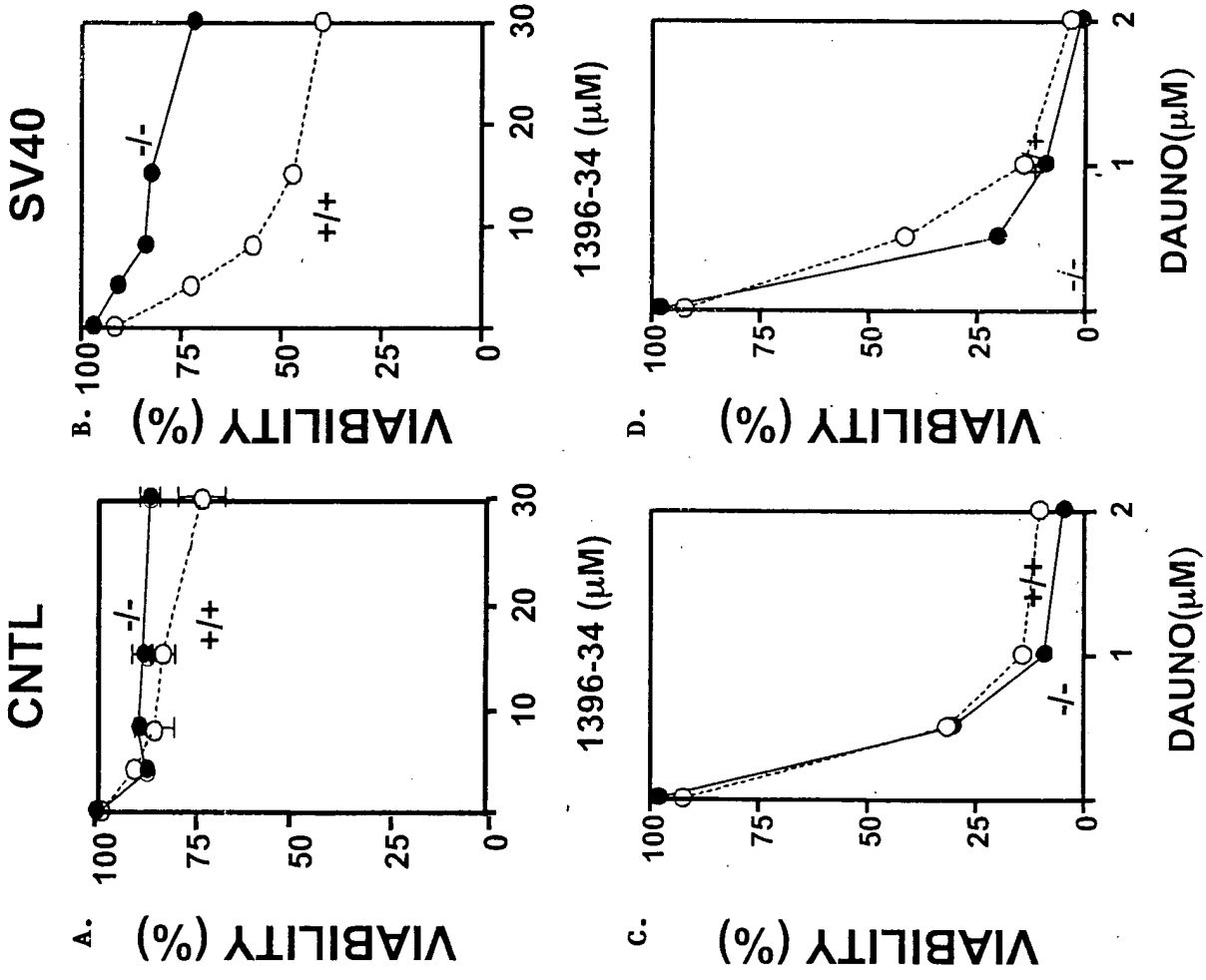

CNTL
SV40
A.
B.
C.
D.
VIABILITY (%)
1396-34 (μM)
DAUNO(μM)
-/-
+/+
0
25
50
75
100
10
20
30
1
2

FIGURE 38

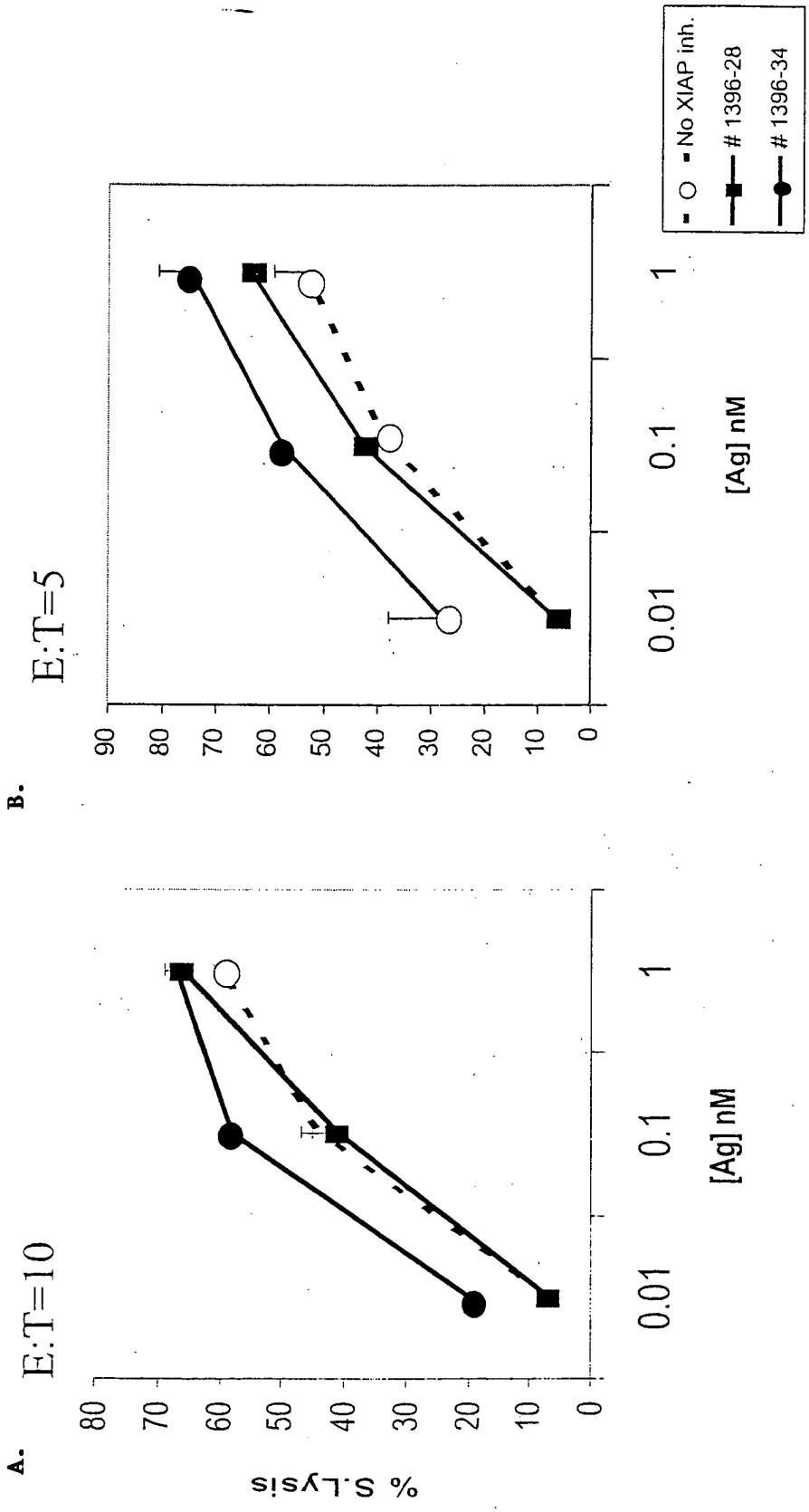

A.
E:T=10
% S.Lysis
80
70
60
50
40
30
20
10
0
0.01
0.1
1
[Ag] nM
B.
E:T=5
90
80
70
60
50
40
30
20
10
0
0.01
0.1
1
[Ag] nM
No XIAP inh.
1396-28
1396-34

FIGURE 39

A.

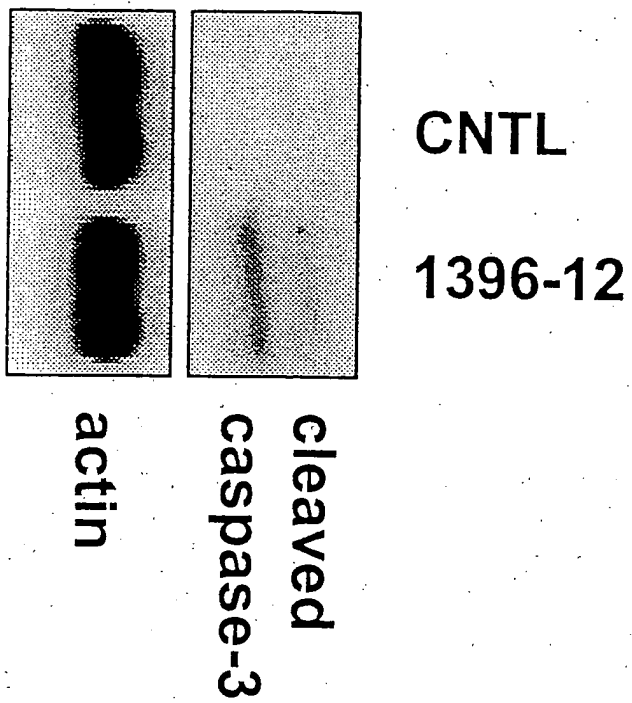


FIGURE 40

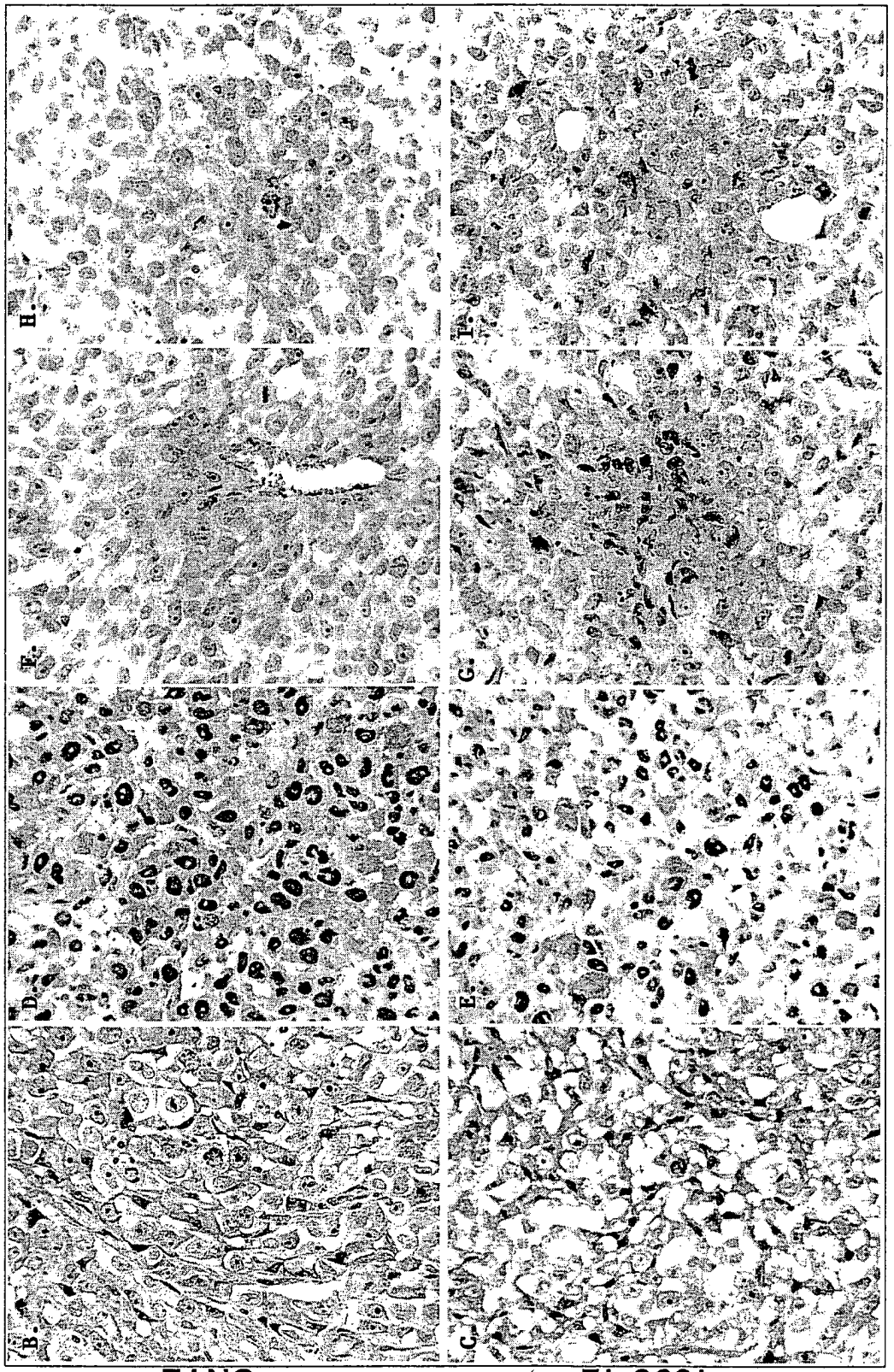


FIGURE 40 (cont.)

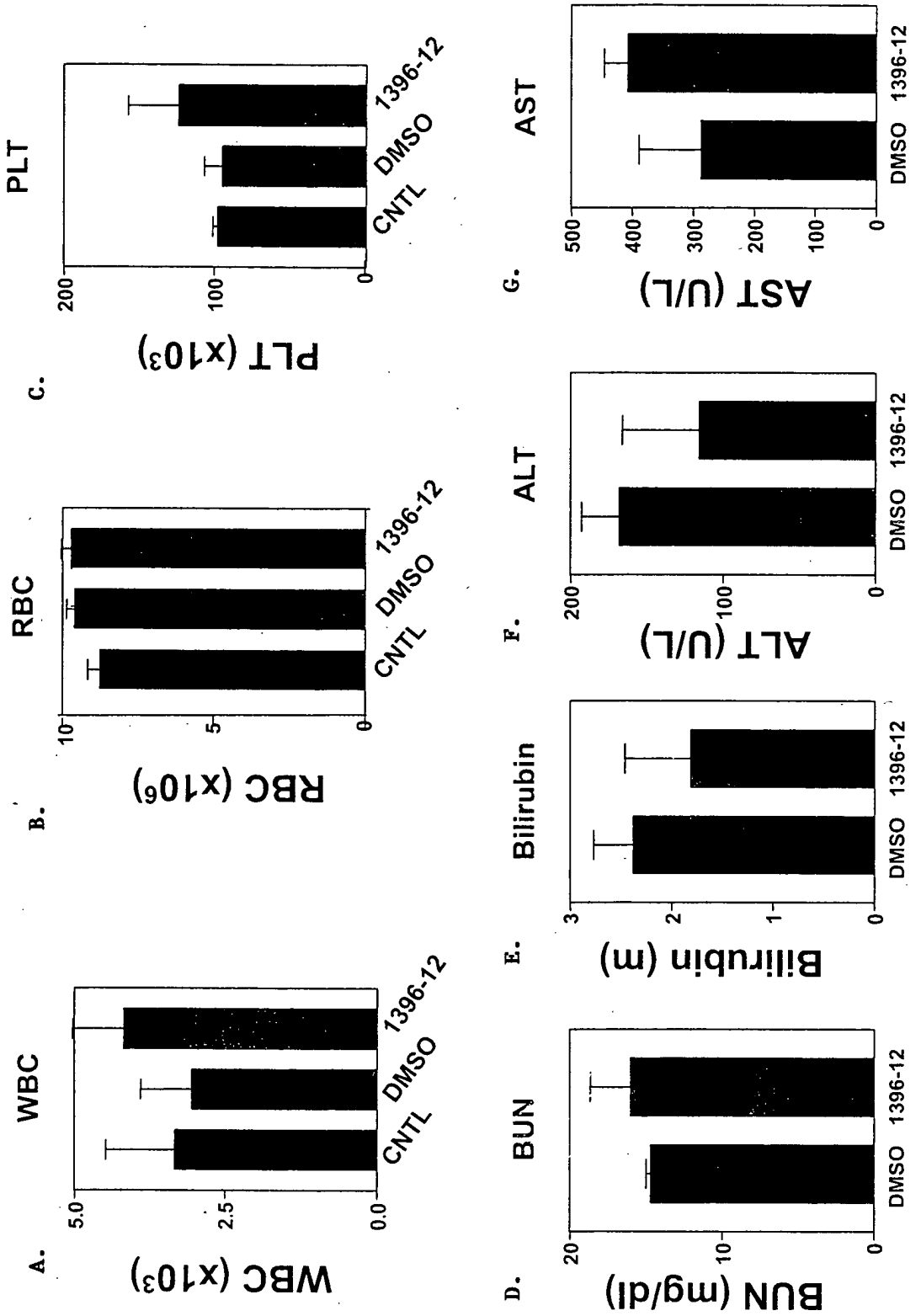

A.
WBC
WBC (x10³)
5.0
2.5
0.0
CNTL
DMSO
1396-12
B.
RBC
RBC (x10⁶)
10
5
0
CNTL
DMSO
1396-12
C.
PLT
PLT (x10³)
200
100
0
CNTL
DMSO
1396-12
D.
BUN
BUN (mg/dl)
20
10
0
DMSO
1396-12
E.
Bilirubin
Bilirubin (m)
3
2
1
0
DMSO
1396-12
F.
ALT
ALT (U/L)
200
100
0
DMSO
1396-12
G.
AST
AST (U/L)
500
400
300
200
100
0
DMSO
1396-12

FIGURE 41

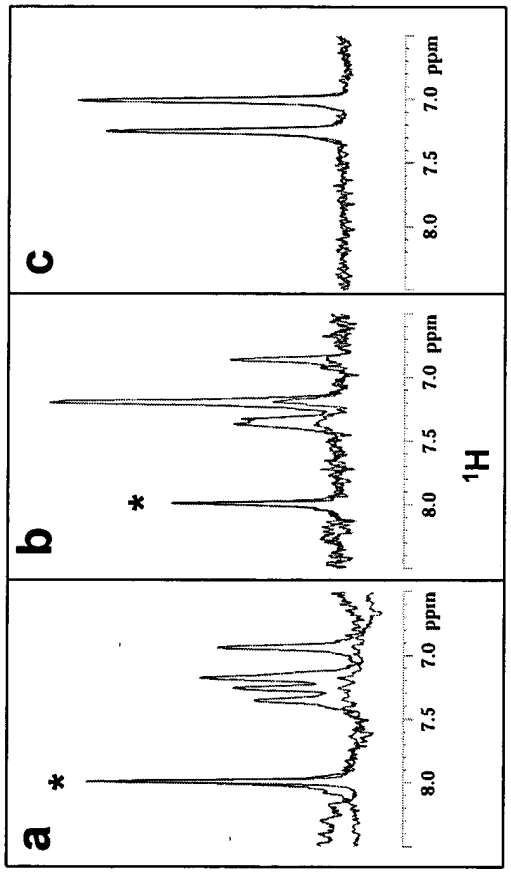


FIGURE 42

TPI 1453						MW	XIAP-FL derepression data [lowest ratio 1.8]	AVG IC-50 uM	STD	Competitive binding assay IC-50 uM	STD
1	L-Thiala	L-Nal	pCl-L-f	Lys eFm	$-NH_2$	900.9	**12.5**	**21.0**	10.3	**48.4**	10.0
2	**G**	L-Nal	pCl-L-f	Lys eFm	$-NH_2$	803.7	**6.25**	**14.1**	0.6	**10.1**	9.0
3	L-Thiala	**G**	pCl-L-f	Lys eFm	$-NH_2$	759.5	**~100**	**~131.7**		**57.7**	15.6
4	L-Thiala	L-Nal	**G**	Lys eFm	$-NH_2$	775.2	**25**	**69.0**		**38.5**	16.4
5	L-Thiala	L-Nal	pCl-L-f	**G**	$-NH_2$	607.3	**>100**	**> 164.7**		**>165**	na
6	L-Thiala	L-Nal	dLysFm	Lys eFm	$-NH_2$	1068.8	**3.13**	**6.1**	2.1	**12.6**	4.8
7	**G**	L-Nal	dLysFm	Lys eFm	$-NH_2$	971.6	**6.25**	**36.4**	16.7	**4.2**	1.1
8	L-Thiala	**G**	dLysFm	Lys eFm	$-NH_2$	927.4	**3.13**	**24.0**	1.7	**7.1**	6.9
4	L-Thiala	L-Nal	**G**	Lys eFm	$-NH_2$	775.2	**25**	**69.0**		**38.5**	16.4
9	L-Thiala	L-Nal	dLysFm	**G**	$-NH_2$	775.2	**6.25**	**19.0**	8.6	**3.8**	3.6
TPI 1237-1	Smac 7 mer					724.4				**18.8**	4.0
TPI 1425-1	Smac 4 mer					397.2				**30.3**	

TPI 1453-1=TPI 792-33 and TPI 1408-3
TPI 1453-6=TPI 792-35

FIGURE 43

TPI 1554 Bi tinylated Tetrapeptides

TPI 1554 #	Non-Biotin Synthesis #	Sequence	1	2	3	4	5	6	7		MW
TPI 1554-1	TPI 792-33, TPI 1408-3,TPI 1453-1	H-	L-Thiala	L-Nal	pCl-L-f	Lys eFm	(Biotin	6aha)	Kboc/fmoc	-NH2	1365.6
TPI 1554-2	TPI 792-35, TPI 1453-6	H-	L-Thiala	L-Nal	dLysFm	Lys eFm	(Biotin	6aha)	Kboc/fmoc	-NH2	1534.7
TPI 1554-3	TPI 1332-4	H-	Boc-L-Ala	Boc-L-Trp(CHO)	Boc-L-Trp(CHO)	Boc-D-Nal	(Biotin	6aha)	Kboc/fmoc	-NH2	1124.5
TPI 1554-4	TPI 1332-41	H-	Boc-L-Cha	Boc-D-Nal	Boc-L-Trp(CHO)	Boc-L-ThiAla	(Biotin	6aha)	Kboc/fmoc	-NH2	1173.6
TPI 1554-5	TPI 1332-69	H-	Boc-L-Nal	Boc-D-Cha	Boc-D-Phe	Boc-L-ThiaAla	(Biotin	6aha)	Kboc/fmoc	-NH2	1134.6
TPI 1554-6	TPI 1332-77	H-	Boc-L-Nal	Boc-D-plPhe	Boc-D-Phe	Boc-L-ThiaAla	(Biotin	6aha)	Kboc/fmoc	-NH2	1254.4
TPI 1554-7	TPI 1495-19	H-	L-Nal	pCl-L-f	Lys eFm	(Biotin	6aha)	Kboc/fmoc		-NH2	1212.6
TPI 1554-8	TPI 1495-20	H-	L-Thiala	L-Nal	dLysFm	(Biotin	6aha)	Kboc/fmoc		-NH2	1184.6

FIGURE 44

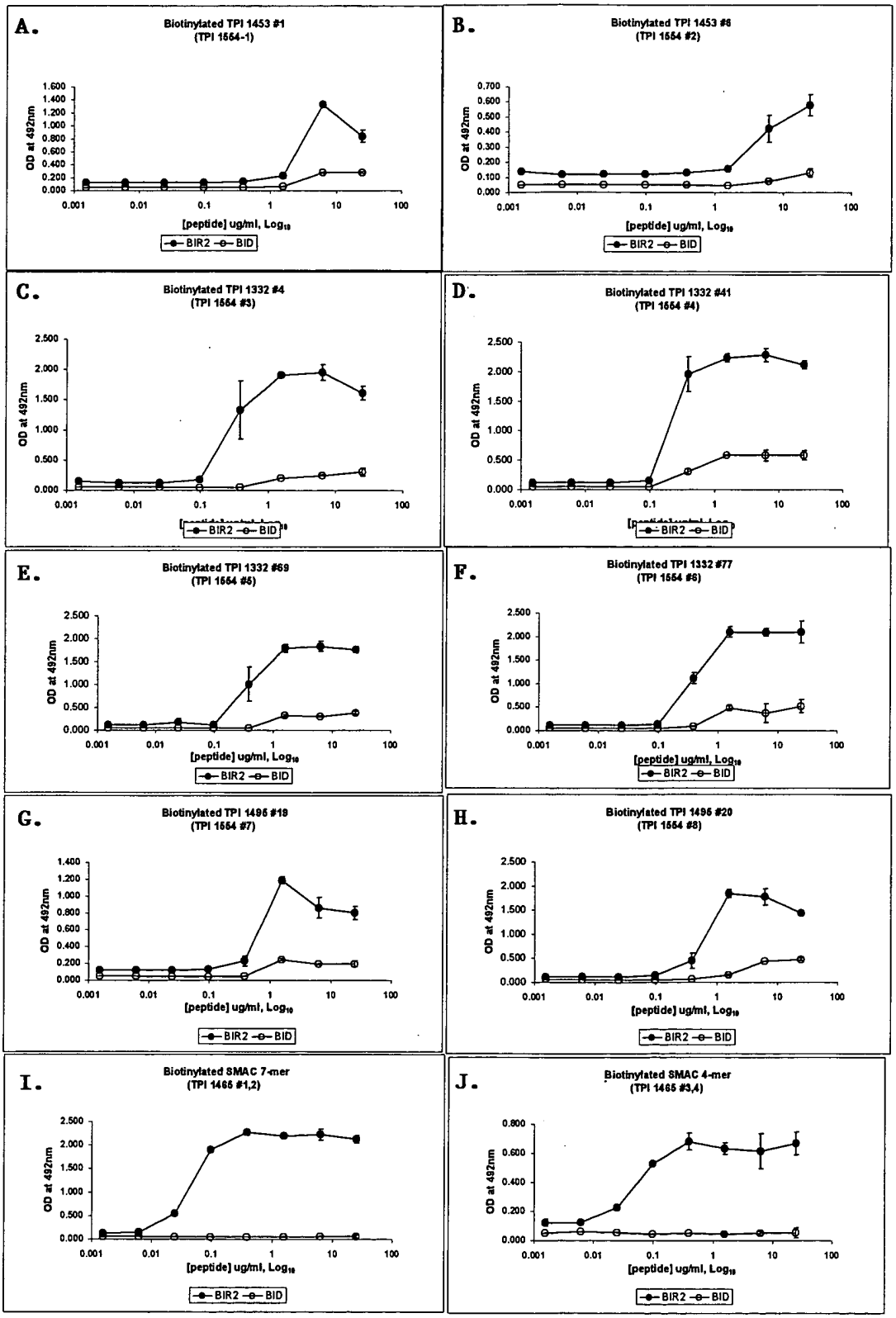

Binding of XIAP-BIR2-GST and BID-GST to Biotinylated Tetrapeptides
A.
Biotinylated TPI 1453 #1
(TPI 1554-1)
B.
Biotinylated TPI 1453 #6
(TPI 1554 #2)
C.
Biotinylated TPI 1332 #4
(TPI 1554 #3)
D.
Biotinylated TPI 1332 #41
(TPI 1554 #4)
E.
Biotinylated TPI 1332 #69
(TPI 1554 #5)
F.
Biotinylated TPI 1332 #77
(TPI 1554 #6)
G.
Biotinylated TPI 1496 #19
(TPI 1554 #7)
H.
Biotinylated TPI 1496 #20
(TPI 1554 #8)
I.
Biotinylated SMAC 7-mer
(TPI 1465 #1,2)
J.
Biotinylated SMAC 4-mer
(TPI 1465 #3,4)
OD at 492nm
[peptide] ug/ml, Log10
BIR2
BID

FIGURE 45

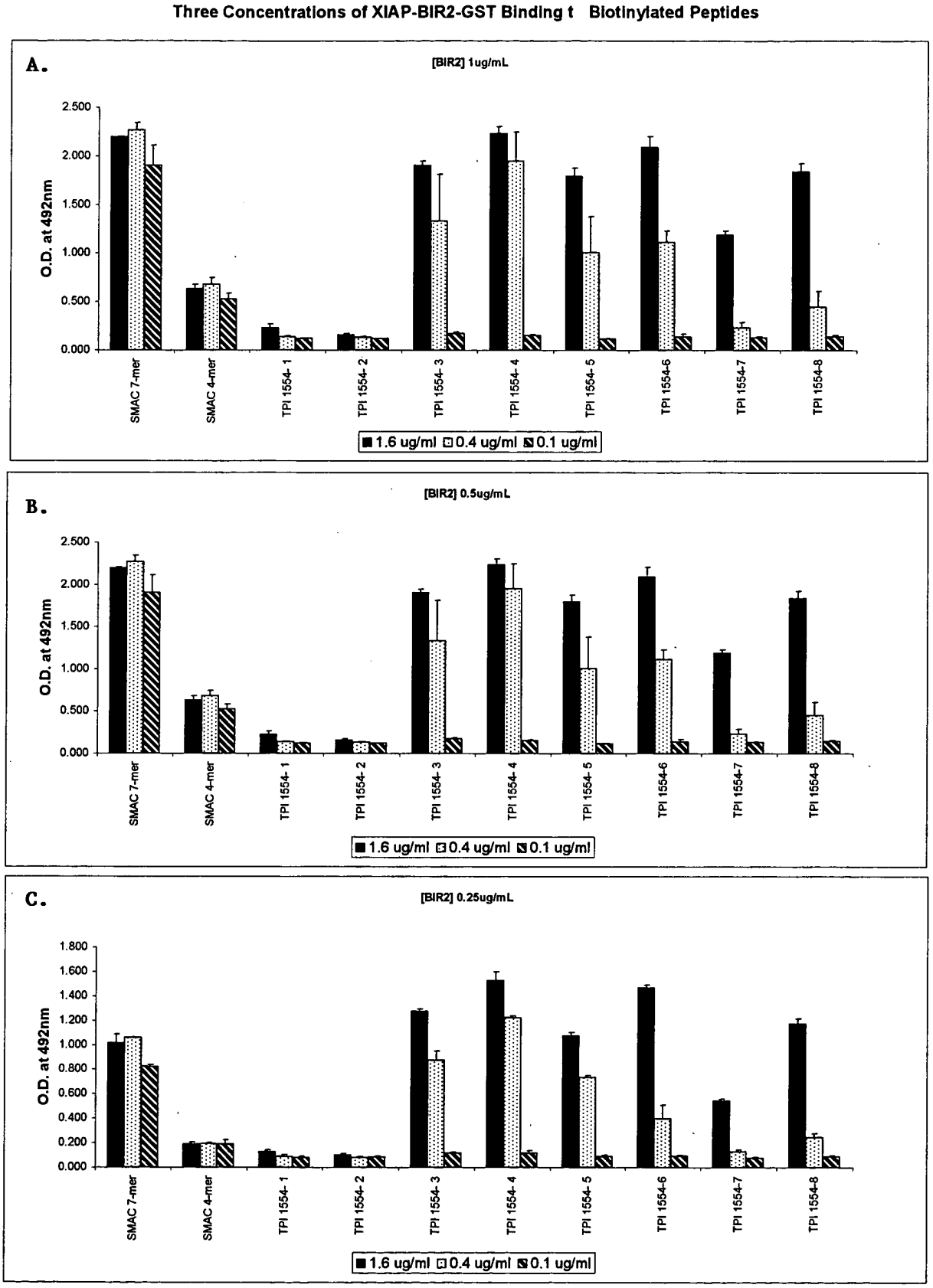
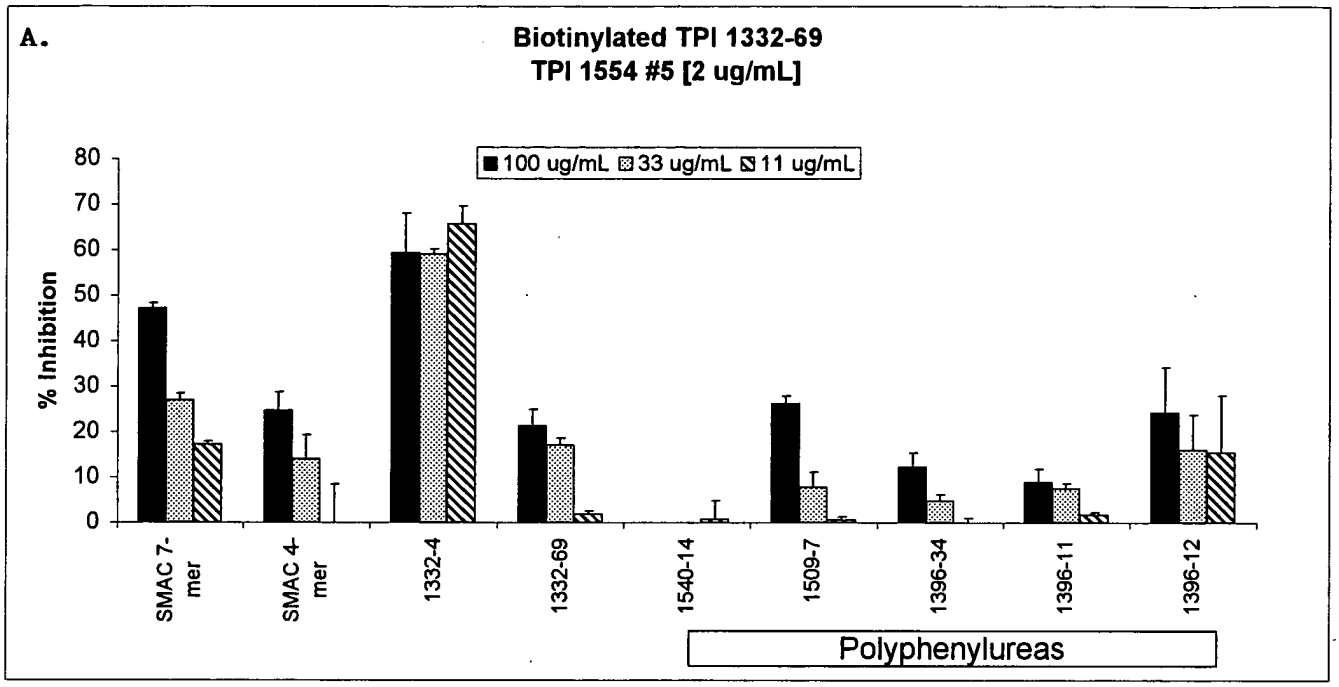

Three Concentrations of XIAP-BIR2-GST Binding t Biotinylated Peptides
A.
[BIR2] 1ug/mL
O.D. at 492nm
2.500
2.000
1.500
1.000
0.500
0.000
SMAC 7-mer
SMAC 4-mer
TPI 1554- 1
TPI 1554- 2
TPI 1554- 3
TPI 1554- 4
TPI 1554- 5
TPI 1554-6
TPI 1554-7
TPI 1554-8
1.6 ug/ml 0.4 ug/ml 0.1 ug/ml
B.
[BIR2] 0.5ug/mL
O.D. at 492nm
2.500
2.000
1.500
1.000
0.500
0.000
SMAC 7-mer
SMAC 4-mer
TPI 1554- 1
TPI 1554- 2
TPI 1554- 3
TPI 1554- 4
TPI 1554- 5
TPI 1554-6
TPI 1554-7
TPI 1554-8
1.6 ug/ml 0.4 ug/ml 0.1 ug/ml
C.
[BIR2] 0.25ug/mL
O.D. at 492nm
1.800
1.600
1.400
1.200
1.000
0.800
0.600
0.400
0.200
0.000
SMAC 7-mer
SMAC 4-mer
TPI 1554- 1
TPI 1554- 2
TPI 1554- 3
TPI 1554- 4
TPI 1554- 5
TPI 1554-6
TPI 1554-7
TPI 1554-8
1.6 ug/ml 0.4 ug/ml 0.1 ug/ml

FIGURE 46

Comp tition for the Binding of Biotinylated Tetrapeptides with XIAP-BIR2-GST



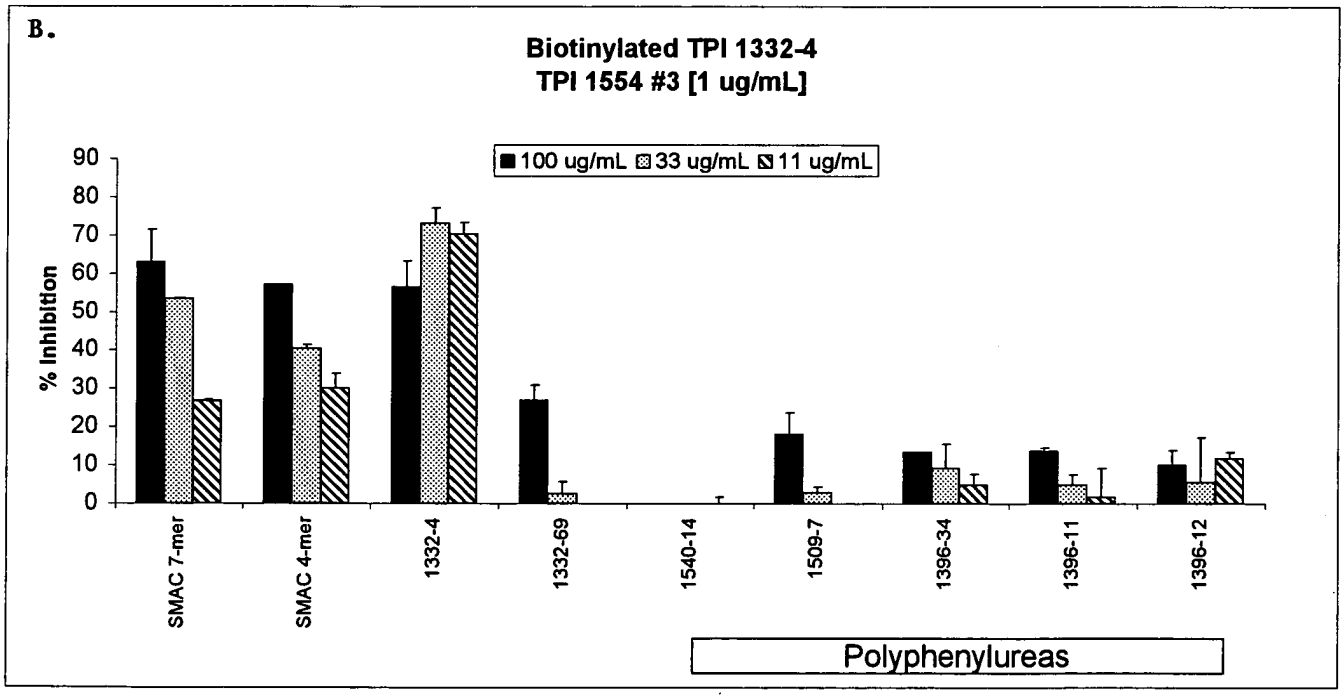


FIGURE 47